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Simulation of the effects of Alzheimer's disease on medication regimen compliance

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**SIMULATION OF THE EFFECTS OF
ALZHEIMER'S DISEASE ON
MEDICATION REGIMEN COMPLIANCE**

A Thesis

Presented to

The Faculty of the Program in Human Factors/Ergonomics

San Jose State University

In Partial Fulfillment

Of the Requirements for the Degree

Master of Science

By

Mark J. Williams

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ABSTRACT

SIMULATION OF THE EFFECTS OF ALZHEIMER'S DISEASE ON MEDICATION REGIMEN COMPLIANCE

by Mark J. Williams

This paper discusses simulated administration of medication regimens by a healthy elderly population and a population affected by very mild Alzheimer's disease.

Models were constructed to simulate regimens of one and three doses per day. The models contained networks of tasks and actions germane to medication administration. Human performance was simulated by probability and rule-based transitions between tasks. The transitions represented cognitive operations utilized during medication regimen administration. The parameter values used in the models were based on a review of neuropsychological test data for analogous cognitive operations.

The models were validated by comparing the simulation results of the healthy elderly population with regimen compliance data from a real population. Manipulating the parameter values of the models generated predictive data for the Alzheimer's disease population. The data generated by the simulations suggested that very mild Alzheimer's disease would significantly impair an individual's ability to administer a medication regimen.

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INTRODUCTION AND REVIEW

Medication Administration Overview

Self-administration of medication is a daily activity for most senior citizens and can have life-threatening consequences if not done correctly. Up to one-third of elderly (65+) admissions to hospitals are associated with drug regimen problems (Frisk, Cooper, & Campbell, 1977). In addition, approximately 40% of people entering nursing homes do so because they are unable to self-medicate (Lieberman & Kramer, 1991).

Noncompliance, both intentional and unintentional, is the dominant factor in drug regimen problems, resulting in adverse drug reactions, underuse, and overuse. Estimates of medication regimen noncompliance among the elderly range from 40% to 75%, with most estimates at 50% (Salzman, 1995). Noncompliance has been estimated to add from \$20-100 Billion annually to the U.S. health care bill (Tucker, 1993). Among the factors statistically associated with higher risk of hospitalization due to noncompliance are poor recall of medication regimen and use of numerous medications. Park, Willis, Morrow, Diehl, and Gaines (1994) have reported that 34% of elderly individuals are taking three or more prescribed medications concurrently. Additionally, significantly higher rates of noncompliance were found among the elderly living alone (Col, Fanale, & Kronholm, 1990).

Significant factors contributing to poor recall of medication regimen are normal aging of memory and cognitive impairments such as dementia (Cooper, 1994). Of dementia-related disorders, dementia of the Alzheimer type (DAT) is the most common,

accounting for approximately 66% of all dementia and currently affecting approximately 4,000,000 people in the United States (Roth, 1993). This accounts for three percent of the population from 65-74, 18.7 % of people from 75-84 and nearly 50% of people over the age of 85.

The exact cause or causes of Alzheimer's disease are not known yet, and there is no cure for the disease. At the time of this writing, pharmaceutical and biotechnology treatments have succeeded only in addressing symptoms of the disease and, at best, temporarily slowing its progression (Knopman & Morris, 1997).

As the "baby-boomer" generation reaches seniority in the upcoming two decades, there will be more people over the age of sixty-five in the United States than any other age group (U.S. Senate, 1988). It is statistically likely that the prevalence of AD will increase in conjunction with this population. Additionally, people are living longer, increasing the likelihood that a large percentage of the population will live to be at least 85. Many of these people will be living alone, without consistent support from a relative or caregiver, and up to 85% will be responsible for administering their own medications (Law & Chalmers, 1976).

Medication Aids Overview

Medication administration aids are a strategy used to supplement regimen recall, and are widespread in their use and proven effectiveness (Laster, Martin, & Fleming, 1996; Lierer, Morrow, Tanke, & Pariente, 1991; Wandless & Davie, 1977). Types of aids include ad-hoc approaches like reminder notes and household alarm clocks, commonly

available items like time or date-based pill organizer trays, blister packs, telephone-based voice mail systems, and electronic devices that integrate alarms, instruction, and pill storage and dispensation. However, the lack of research on the effectiveness of existing or proposed medication administration aids as they apply to demented individuals at various stages of disease development is of particular concern in light of the prevalence of dementia-related disorders among the elderly (Roth, 1993).

One reason for the lack of research is the inherent difficulty in studying declining clinical populations over time. The cognitive capabilities of individuals with Alzheimer's disease progressively deteriorate, at first rendering them incapable of performing complex and concurrent tasks (Salthouse, 1991) and eventually even simple ones such as combing one's hair (Myers, 1995). A medication administration aid that is effective for an individual at an early stage of the disease will become less effective and eventually useless as the disease progresses. Gathering longitudinal data is problematic since one cannot expect the subjects to perform consistently over time periods as short as hours. Another hurdle is accessing the population that would most likely benefit from aid strategies: those in the early stages of the disease. Most people in the early stages of the disease have not yet been diagnosed as having AD, and are therefore difficult to target on an individual basis without first conducting random population sampling, an expensive and time consuming undertaking. Finally, for products in development, the established process of testing concepts, refining, re-testing, and so on is not well supported by traditional experimental methods due to their substantial time and economic commitments.

Human-Machine Systems Modeling

Clearly, there is a need to evaluate existing and proposed designs for medication administration aids to be used by populations suffering from dementia and yet, clear methodological problems in doing so. What is needed is the ability to provide focus for experimental validation of existing or proposed medication administration aids and then coordinate the findings in context to understand the larger, whole system implications. We propose that this can be done by creating a series of computer-based simulation models of medication regimen compliance. The models define successful goal attainment as the result of total system performance, where the system is comprised of all factors related to the activity, e.g., the human participant, the goals and task structure of the activity, the complexity of the regimen, time, environmental conditions, and the augmentative strategy. This approach allows multiple factors to be easily manipulated in order to assess their impact on goal attainment. This can result in a significant savings of time and cost in comparison with more traditional development processes that rely solely on the prototyping/testing cycle (Gansler, 1987, 1995). The types of variables manipulated by these models are task completion times, error rates, effects of environmental interference, and of particular interest to this study, effects of cognitive impairments and medication regimen complexity.

Theoretical Background. Corker (1999) characterized human-machine systems modeling work by Craik (1947) as providing three legacies pertinent to current research:

- 1) A way to describe humans and machines in collaboration in the same mathematical, structural, and dynamical terms
- 2) Analytic capability to define what and when information should be displayed to the human operator in the system as a consequence of their sensory, perceptual and cognitive characteristics relative to the performance of the system
- 3) The ability for human-machine systems to be conceptualized as a single entity linked/coupled to perform a specific task or set of tasks. A new level of abstraction was introduced and systematized by Craik and subsequent developers of operator control models. In this paradigm, the description the operator in the human-machine system could be used to guide the machine design. Further, the linked system could be used to explore the parameters of human performance, i.e., by changing the characteristics of the machine the scientist could observe the human's response and infer something about the characteristics of the human operator.

These legacies provide the underpinning for simulation studies leveraging existing human performance data that generate *predictive* rather than just *descriptive* data in advance of actual artifact availability. This use of modeling and simulation allows a fundamental shift in the design process for unique systems or artifacts. Instead of reliance on testing of artifact prototypes after they have been extensively defined, one can use predictive data generated from simulation and modeling of human-machine systems engaged in representative tasks to iteratively refine conceptual designs before committing to time-consuming and costly prototyping. Using Monte Carlo simulation techniques,

each scenario can be run many times, providing the data for a statistical distribution for the human-machine performance for that system configuration and activity domain.

It is important to note that simulation should not be considered a replacement for traditional experimentation and development methods. The nature of models is that they are inexact representations of actual events and processes that will always contain some error. To this end, as a product or system moves through the design process, human factors and ergonomics designers will often want to confirm and enhance modeling and simulation predictions with prototyping and experimentation. In essence, simulation provides a means of extending the knowledge base of human factors and amplifying the effectiveness of experimentation (Laughery & Corker, 1997).

Task Network Models. A task network model is a sequential representation or mapping of behavior of an individual performing a function, and provides the structural framework for behavior analysis and prediction. The purpose is to achieve a goal, described as a desired system state (Preece, et al., 1994). The goal can be generated by an agent performing the function, where an agent is any rational system. For example, an individual who wishes to take medication and an electronic device designed to alert, dispense, and track medication can both be viewed as agents that share a common goal. In this case, agent interaction is requisite to successfully achieving a goal.

A goal is achieved by using some device that is able to facilitate transition to the desired state. Given that a goal exists, an agent chooses a device that will enable goal achievement. Once the device has been selected, the tasks necessary to accomplish the

goal are understood. These are prescribed by the logical structure and functioning of the device. Thus, a task is defined as a portion of the activities required, used, or believed to be necessary to achieve a goal using a particular device or combination of devices. The tasks can be ordered into a sequential network, with rules or probabilities determining the transitional relationships between the tasks.

A task can be decomposed into sub-tasks in which activities are undertaken in some sequence. The sub-tasks can contain their own models, such as a description of the elements of knowledge a user can have about the tasks they are performing, to a description of the pertinent features of the physical environment in which the tasks are performed. The outputs of the tasks are actions that initiate change in the task environment. In skilled behavior, actions can be viewed as relatively automatic, requiring no problem solving or control structure component. On the other end of the continuum is unskilled behavior, where the same actions can be iterative processes that rely heavily on problem solving. Representation of cognitive processes such as problem solving or knowledge status requires a detailed representation of human performance within the structure of the task network model.

Human Performance Models. Of the constituents that make up a medication administration system model, definition of the human dimension of the model is the most difficult, since model complexity is a subjective decision and all theories of cognition are constructs. Given these assumptions, to provide a relatively complete and useful representation of the human operator in the model, the following three aspects of operator

behavior need to be accounted for: perceptual processes, cognitive processes, and output processes (Corker, 1999).

A fundamental assumption that allows representation of human behavior in models is that the human mind is an information processor. Doing this allows the creation of structures and processes that have definable limits and principles of operation. In the *Model Human Processor* Card, Moran, and Newell (1983), represent human information processing as approximated by sequential sets of perceptual and motor processors surrounding a cognitive processor. A theory underlying most, if not all, current human performance models is that cognitive processes draw upon multiple resources that can be represented as semi-distinct channels with finite capacities (Wickens, Sandry, & Vidulich, 1983). As tasks are performed, demands particular to the task are placed on the channels and they “fill-up” or become loaded. Choosing the pertinent factors to model thus calls for a taxonomy of skills identified for each task. These skills necessarily demand resources that have been represented as “cognitive workload” values (McCracken & Aldrich, 1984) for perception (vision, auditory, and attention), processing (long term memory, working memory, and central executive), and output (motor control, voice command). As an example, a scale used for visual attentional demands is shown below:

Value: Activity:

1	Monitor, scan, survey
2	Detect movement, change in size or brightness
3	Trace, follow, track

- 4 Align, aim, orient
- 5 Discriminate symbols, numbers, words
- 6 Discriminate based on multiple aspects
- 7 Read, decipher text, decode

Similar scales have been developed for the auditory, cognitive, and psychomotor channels, and substantial data have been gathered and validated to estimate the workload of each channel for particular tasks. By using this approach, each task can be characterized as placing a burden on one, some, or all of the channels represented with a value between one and seven. Total operator workload is calculated by summing the burdens simultaneously placed on each channel during a specified period. During this period, the individual may perform multiple tasks concurrently, which can increase total workload. If the total workload is equal to or exceeds a defined threshold (in this case, 8), the individual can choose to eliminate a task or tasks to reduce workload, or accept some risk of performance degradation.

To simulate non-optimal performance, such as complex problem solving while fatigued, dynamic ranges of decrement can be applied to each functional channel (e.g., perception, processing, output) as “stressor” functions (LaVine, Laughery, & Peters, 1995). The degradation functions quantitatively link skill performance to the level of a stressor. The functions can be developed from any data source, including standard test batteries or actual human tasks (Laughery & Corker, 1997). These functions map the performance decrement expected on a skill based on the parameters of the performance shaping factor (e. g., time since sleep). For instance, a task that placed a burden of 4.3 workload units on the cognitive channel during normal performance might place a burden

of 5.6 workload units on the cognitive channel if the individual has gone without sleep for 48 hours. It is our belief that similar “stressor” functions applied to differentiated cognitive operations can be used to represent dementia. This could be implemented simply as a lower probability for remembering a particular piece of information, and would be based on clinically gathered neuropsychological test data for operations similar to the ones represented in the model.

Validation, Verification, and Testing. A key component of any successful simulation is the validation, verification, and testing (VV&T) of the model to assure that it is representative of the real-world process being simulated. Balci (1994) provides a review of when in model development VV&T should be conducted and what evaluative methods are available at each phase.

Validation is substantiating that the model behaves with satisfactory accuracy consistent with the study objectives within its domain of applicability. In essence, it is about building the *right* model. It is conducted by running the model under the same input conditions expected in the real system and comparing model behavior with system behavior. A multivariate comparison can be carried out to incorporate correlation among the output variables. Model verification is substantiating that the model is transformed from one form into another, as intended, with sufficient accuracy. Model verification is building the model *right*. The accuracy of transforming a problem formulation into a model specification or executable computer program is evaluated in verification. Model

testing reveals errors in the model, can iterate through many cycles, and is conducted to perform validation and verification.

Model VV&T is employed to prevent the occurrence of three major types of errors in simulation studies: Type I error is the error of rejecting the model credibility when in fact, the model is credible. Type II error is accepting model credibility when in fact, the model is not sufficiently credible. Type III error is the error of solving the wrong problem. Model VV&T techniques range from informal methods, such as peer reviews, to complex formal methods such as predicate calculus. The techniques appropriate for each stage of model development are different and may be subjectively applied, and will be discussed in greater detail in the simulation methods, results, and discussion sections.

Medication Regimen Compliance

The most commonly used definition of compliance is “the extent to which a person’s behavior (in this case, taking medications) coincides with medical or health advice” (Haynes, Taylor, & Sackett, 1979). Compliance is not binary. It is judged on a percentage basis, with acceptable rates varying considerably for different regimens. The potential impact on the health of the patient is the determining factor in the assessment of acceptable levels of both measures of compliance. Unfortunately, given the frail health of many elderly individuals, even slight deviations from perfect compliance can have serious consequences.

Behaviors and Contributing Factors. Drug regimen noncompliance can be decomposed into intentional and unintentional noncompliance. The observable behaviors of noncompliance are dose omissions, extra doses (hypercompliance), taking the wrong medication, incorrectly administered doses (too many/too few pills or special conditions such as “take with food” not met), and taking the correct medication at the wrong time (Cooper 1994). Intentional noncompliance can be due to many factors, including unwillingness to endure unpleasant side effects, feelings of futility, cost of medications, perception of lack of medication efficacy, and even a general dislike of taking medication (Col, Fanale, & Kronholm, 1990). The *self regulatory model of medication adherence* (Leventhal & Cameron, 1987) is a synopsis of the influence of non-cognitive, patient-generated factors on compliance and emphasizes the role of patient values, beliefs, and internal illness representation as predictors of how an individual regulates medication taking behavior.

Unintentional drug regimen noncompliance in the elderly is due primarily to faulty memory performance, and is the type of noncompliance that will be simulated in this study. “Forgetting” is the number one factor cited in hospital admissions related to noncompliance among the elderly (Salzman, 1995), though the memory components involved in drug regimen administration are not a unitary function. This will be discussed in detail later in this section.

Many factors have been associated with unintentional noncompliance behavior. The factor that has received the largest amount of clinical attention is the complexity of the medication regimen. Kronke and Pinholt (1990) defined a formula expressing the

complexity of a drug regimen as the number of drugs per patient multiplied by the total number of dose events per day. Of the two components contributing to regimen complexity, the number of dose intervals per day has been the most widely studied and has exhibited consistent results, with fewer dose events per day associated with higher pill count and regimen compliance rates: (Paes, Bakker, & Soe-Agnie, 1997; Cramer, Mattson, Prevey, Scheyer, & Oullette, 1989; Eisen, Miller, Woodward, Spitznagel, & Przybeck, 1990; Kruse & Weber, 1990; Botelho & Dudrak, 1992). Kendrick and Bayne (1982), Botelho and Dudrak (1992) and Hulka, Kupper, Cassel, and Efird (1975) found that an increase in the number of prescription medications taken concurrently decreased regimen compliance, though other studies (Kruse & Weber, 1990; Issac, Tamblyn, & the McGill-Calgary Drug Research Team, 1993) and reviews (Haynes, Sackett, Taylor, Roberts, & Johnson, 1977) do not support these results. One of the difficulties in controlling studies such as these is that an increased number of medications can be associated with lower cognitive performance (Lierer, et al., 1991) and poorer health, which may confound the results if cognitive ability differences across differing regimens is not matched. Other confounding factors exist, such as tablet type, complexity of administration conditions, and severity of illness.

Additional factors contributing to noncompliance behavior are poor drug knowledge, physical limitations, cognitive or behavioral disturbances, poor patient-health professional communication, and psychosocial characteristics such as living alone (Ascione, 1994). Poor drug knowledge and poor patient-health professional communication can be seen as two sides of the same coin; the initial communication

might be too complex to understand, and at a later time, patients can have difficulty remembering the purposes and instructions of multiple medications. Ley (1978) devised a linear regression equation based on observed data that predicted the rate of forgetting of medical information based on information complexity. Physical limitations such as poor eyesight and poor fine motor control impair a patient's ability to read medication container labels and instructions as well as their ability to successfully manipulate the medication container and the medication itself. Cognitive and behavioral disturbances such as dementia or depression play major roles in noncompliance and will be discussed in the following section. Finally, the elderly who live in social isolation make significantly more medication errors and often lack the assistance needed for obtaining and monitoring complex regimens (Cooper, 1994).

Measures and Data Collection. Many measures of compliance exist, and for many years the lack of a "gold standard" measure has made comparisons of compliance rates across different studies difficult. Fortunately, two measures have gained popularity in the last decade and have often been used together: (Paes et al., 1997; Cramer et al., 1989; Eisen et al., 1990; Kruse & Weber, 1990). The first is a simple percentage of total pills prescribed divided by total pills taken and will be referred to as "pill count" from this point forward. The second is a percentage of the total number of days in which all doses were taken as prescribed divided by the total number of days observed, and will be referred to as "regimen compliance" from this point forward. All of the studies listed

showed that both pill count and regimen compliance decreased as the number of dose intervals per day increased.

Pill count is a relatively insensitive measure since it is vulnerable to “multiple dosing” behavior. “Multiple dosing” refers to the practice of taking more than the prescribed number of pills for a particular dose interval. It can be an intentional behavior if, for instance, a patient believes they missed an earlier dose and wants to make up for it. It can also be an unintentional behavior if the patient is confused about the number of pills per dose interval or if they make a simple counting/pill verification error. An extreme example of this effect for a theoretical 6 day regimen is if a patient were to miss 3 days of medication administration and then double dose for the remaining three days of the regimen. The use of pill count alone would reflect a 100% success rate, though it is clear that the efficacy of the regimen is likely to have been decreased by the patient’s behavior. Regimen compliance is therefore the more sensitive measure since it directly measures the rate of compliance with each particular dose interval.

Time deviation from a prescribed dose has also been used a measure of compliance, most notably by Lierer et al. (1991) and Lierer, Morrow, Pariente, and Sheikh (1988). In their work, forgetting to take a pill was scored as the average number of hours between taking pills of that type. Thus, missing one dose of a three times daily dose interval would be scored as an 8.0 hour deviation. Pills that were taken within the prescribed dose interval range but not exactly on time were also added to the measure. Despite identical methods, they reported inconsistent results, with a four times daily dose interval exhibiting significantly higher noncompliance than a once daily interval in one

study and no significant difference in the other study. However, their studies employed a between subjects design where each subject took four simulated medication types (each reflecting a different dose interval), a factor combination which could influence their results. In addition, their studies reported higher compliance than most others previously referred to, which they attributed to a high level of motivation. Finally, the fact that subjects knew they were taking placebo pills and that no true illnesses were being treated must be considered when comparing the results of this study with the studies previously referred to, all of which monitored the use of real medications.

Data collection techniques have also varied across studies, including patient self-reporting, clinician interviews, post-hoc pill counts, and both passive and patient-directed electronic monitoring systems. The recent studies have used passive electronic monitoring systems that measure the number of occasions a pill container is opened/closed and the time intervals between these events. This method of data collection does not confirm that the subject has actually taken the medication, and may overestimate compliance behavior. The degree of overestimation has not been quantified. Unfortunately, other data collection techniques such as patient interviews are even more vulnerable to overestimation of compliance. Though direct observation of behavior would alleviate this possible effect, it has not been widely used due to the logistical constraints.

Cognitive Components. Park (1992) presented a model of cognition used during medication administration that contained four components. It included comprehension of

instructions, use of working memory to integrate the instructions into an adherence plan, remembering what the plan is, and finally, remembering to execute the plan, known as prospective memory. When an individual is administering a medication, they must remember the content of the regimen and whether or not they have taken the medication for that dose interval yet. Levy and Loftus (1983) proposed a model of prospective memory that suggested the probability of an individual successfully completing a pre-planned action is a sum of the joint probabilities of the constituent cognitive processes, including generation of a cue to initiate the action, remembering what the action is, and carrying it out. A task analysis conducted during the current research revealed that the last of these processes can be decomposed to reveal multiple structures that use either long-term or working memory. Provided that the patients correctly understand the medication task to be performed, memory failure in medication administration can occur at several points, including:

- 1) Failure to remember to take medication at the required times.
- 2) Failure to remember if medication has been taken.
- 3) Failure to remember medication location.
- 4) Failure to remember which medication to take.
- 5) Failure to maintain an intention to take a medication once the procedure has been initiated.
- 6) Failure to remember how to take medication.
- 7) Failure to accurately verify medication

The points of failure listed above can be characterized as the following cognitive processes:

- 1) Prospective memory: Remembering to do something in the future.
- 2) Episodic memory: Memory for past actions.
- 3) Semantic recall memory: Self-generated memory for information.
- 4) Semantic recognition memory: Externally prompted memory for information.
- 5) Working memory decay: Maintaining temporary data in working memory.
- 6) Procedural memory: Remembering how to perform an action.
- 7) Working memory stimulus discrimination: Discerning correct and incorrect data.

The following section will examine the impact of Alzheimer's disease on these cognitive processes.

Alzheimer's Disease Overview

Alzheimer's disease is defined as "A progressive and irreversible brain disorder characterized by gradual deterioration of memory, reasoning, language, and finally, physical functioning" (Myers, 1995, p. 34). At first, a person with AD exhibits only minor, almost imperceptible symptoms that are often attributed to other illnesses. The patient may not even be aware that they have the disease. Gradually, the person becomes more forgetful, though impact on lifestyle may seem relatively benign. In fact, one of the

main obstacles in diagnoses of Alzheimer's disease is that the resultant behavior from memory loss caused by the disease appears on the surface to be indistinguishable from typical memory decrements found in a healthy elderly population. However, the differences are apparent in neuropsychological testing throughout the disease and in behavior as the disease progresses.

In support of the research direction of this paper, the discussion in this section will focus on economic impact, assessment methods, cognitive functioning (including memory, attention, perception, and psychomotor function) and the resultant impact upon behavior rather than the biological, metabolic, and chemical etiologies of the disease.

Economic Impact. In addition to the emotional, psychological, and health impact on Alzheimer's patients and their caregivers, Alzheimer's disease has a substantial economic impact on the general public and the families of individuals with the disease. The Alzheimer's Association estimates the cost of the disease in the USA to be from \$80-100 billion each year (Ernst & Hay, 1994). This estimate includes costs of diagnoses, treatment, nursing home care, informal care, and lost income (Hutton & Morris, 1996). Unfortunately, it is at the individual and family level that the economic impact of the disease can be most devastating. The average cost of institutional care for Alzheimer's patients is \$47,000 per year (Welch, Walsh, & Larson, 1992). As mentioned previously, 40% of individuals entering nursing homes do so due to an inability to self-medicate.

Assessment Scales and Disease Progression. Kluger and Ferris (1991) created a classification scheme for the various assessment scales based on the patient

characteristics that the assessments primarily measure. They identified five major categories: (1) comprehensive dementia assessments, (2) neuropsychological tests, (3) global staging methods, (4) measures of the activities of daily living and (5) assessments of non-cognitive behavioral symptoms. The comprehensive scales and neuropsychological tests characterize the core cognitive symptoms of Alzheimer's disease. Global staging measures overall disease severity and are based on clinical signs, symptoms, behaviors, and functions. The activities of daily living scales measure the impact of the disease on the patient's ability to function in specified activities related to independent living, including primarily physical activities such as eating, dressing, and toileting and primarily cognitive activities such as dialing a phone, shopping, and taking medications (Lawton & Brody, 1969). The behavioral scales measure non-cognitive symptoms like irritation, obstinacy, and depression. However, these non-cognitive symptoms are not highly relevant to the present study since they do not have manifestations that would directly impact compliance behavior for the population that will be studied.

The assessment scales developed by Reisberg, Ferris, and colleagues (1982, 1985, 1988), address the first four categories and have been statistically correlated to establish staging/scoring equivalencies between the scales. The scales are organized around a 7-point system that describes discreet stages of disease progression. Transition between stages is ordinal and one-way only. Thus, the specific impairments characteristic of each stage almost always follow the impairments described in the previous stage (Kluger & Ferris, 1991). The scales in total incorporate five axes: (1) concentration, (2) recent

memory, (3) past memory, (4) orientation, and (5) functioning and self-care. The stages, clinical characteristics, lifestyle implications, psychometric concomitants, and approximate time progression in years consist of:

Stage 1: No Cognitive Decline

Clinical Characteristics. Patients appear normal; there is neither subjective nor objective evidence of cognitive deficit.

Lifestyle Implications. None

Psychometric Concomitants. The individual scores on at least 3 of the 5 Guild memory tests are average or above.

Timeframe. Not applicable

Stage 2: Very Mild Cognitive Decline

Clinical Characteristics. This is the phase of forgetfulness. Patients in this phase complain of misplacing familiar objects and forgetting the names of familiar people. There is no objective evidence of memory deficit in the clinical interview.

Lifestyle Implications. Minor; patients are aware of a problem.

Psychometric Concomitants. The patient performs below average for their age on 3 of the 5 Guild memory sub-tests.

Timeframe. 3-7 years.

Stage 3: Mild Cognitive Decline

Clinical Characteristics. Clear deficits appear at this stage. There is objective evidence of memory deficits and in some cases, concentration deficits. The patient at this stage may read a passage in a book and retain relatively little material.

Lifestyle Implications. Decreased performance is evident in demanding employment and social situations. Valuable objects may be regularly lost. Extensive instructions on medication administration procedures are unlikely to be recalled. Mild to moderate anxiety often accompanies these symptoms, especially if the patient is required to maintain a level of performance similar to a healthy individual.

Psychometric Concomitants. The patients perform at least a standard of deviation below the average for their age group on at least 3 of the 5 Guild memory sub-tests.

Timeframe. 3-7 years.

Stage 4: Moderate Cognitive Decline

Clinical Characteristics. This is the late confusional stage, and clear subjective and objective deficits are apparent during clinical evaluation. Concentration deficits are seen if patients are asked to perform serial subtractions. Patients display decreased knowledge of recent events in their own lives. At this stage, patients can no longer perform complex tasks accurately or efficiently.

Lifestyle Implications. Ability to travel alone to unfamiliar environments is noticeably curtailed as is ability to manage personal finances.

Managing medication regimens with any level of complexity is unlikely without assistance.

Psychometric Concomitants. At this stage, patients almost always make 3 or more errors on the mental status questionnaire.

Timeframe. 2 years.

Stage 5: Moderately Severe Cognitive Decline

Clinical Characteristics. This is the phase of early dementia. Patients can no longer function without assistance. In addition to memory and concentration, higher cognitive functions such as judgement are impaired.

Lifestyle Implications. Patients may clothe themselves improperly on occasion, be disoriented to time, and are unable to recall a significant aspect of their daily lives.

Psychometric Concomitants. Substantial deficits are apparent on the mental status questionnaire.

Timeframe. 1.5 years.

Stage 6: Severe Cognitive Decline

Clinical Characteristics. This is the middle phase of dementia. The patients may occasionally forget the name of their spouses, and are largely unaware of all recent experiences and events in their lives.

Lifestyle Implications. Patients at this stage will require substantial assistance with physical activities of daily living. For example, they may become incontinent. Personality and emotional changes occur at this stage. They are quite variable and might include delusions, obsessive symptoms, anxiety, agitation, and loss of will necessary to carry out a train of thought.

Psychometric Concomitants. The patients make 5-10 errors on the mental status questionnaire.

Timeframe. 2.5 years

Stage 7: Very Severe Cognitive Decline

Clinical Characteristics. This stage is representative of late dementia. All verbal abilities are lost, they are usually incontinent, and lose gross psychomotor skills, such as walking.

Lifestyle Implications. The patient is unable to initiate meaningful actions and is likely to be bedridden in a partially catatonic state.

Psychometric Concomitants. Patients often make 10 or more errors on the mental status questionnaire.

Timeframe. 6 years.

The mental status questionnaire (Kahn, Goldfarb, & Pollack, 1960) referred to in the previously described disease stages and similar tests such as the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) are general-purpose tests that

evaluate orientation, attention and calculation, immediate and delayed recall, and language abilities. They are valuable in gauging overall level of cognitive performance but have been shown to be relatively insensitive measures during the early stages (1-4) of the disease (reference).

The Guild memory tests (Gilbert & Levee, 1971) referred to in the previously discussed stages are designed to test five expressions of short term memory: (1) Immediate recall of meaningful verbal material, (2) Delayed recall of meaningful verbal information, (3) Immediate recall of newly formed associations, (4) Delayed recall of newly formed associations, and (5) Memory span for non-verbal material. The rationale of the Guild memory tests is that memory is a multi-dimensional function that can not be adequately portrayed by a single measure. In fact, memory tests conducted throughout the course of Alzheimer's disease reveal a heterogeneous pattern of deficits across different memory structures, which will be discussed in greater detail in the following section.

There is some contention over the rate of Alzheimer's disease progression, with evidence emerging to support a non-linear rate of decline. Typically, rates of decline at either temporal end (stages 1, 2, 3 and 7) of disease progression are gradual, taking place over a number of years. The rate of decline during the middle stages (4, 5, and 6) of disease progression is much faster, with changes in behavior apparent on a scale of months or even weeks. However, the heterogeneity of progression among individuals makes prediction of length of time at a particular "functional plateau" impossible. Ortoft and Crystal (1989) propose a linear rate of progression of 4.1 Blessed points (a battery of

neuropsychological tests associated with global staging of Alzheimer's disease) per year, though this is an average of tests taken relatively early and late in the disease, raising the possibility that the proposed rate is not sensitive to more granular progression rates during the middle stages. Teri, Hughes, and Larson (1990) also propose a linear rate of decline of 2.7 MMSE points/year, although this was derived from only two data points gathered two years apart. In addition, the subjects started out with a mean score of 22, indicating that they were already in late stage 3 according to the Reisberg and colleagues scales. This decline was for patients with no history of alcohol abuse, other neurologic impairments, or observable agitation during the interviews. Of interest in this study were the very different rates of decline for individuals with a history of alcohol abuse (7.7 MMSE points/year). While rates of disease progression vary between individuals, perhaps the most important fact of disease progression is that person with Alzheimer's disease can rapidly transition from a state of relative functional autonomy to one of dependence.

Memory. Due to its ubiquity in almost every aspect of complex cognitive functioning, the core symptom of cognitive deficiency in Alzheimer's disease is the loss of memory, which is among the first noticeable signs of the disease (Welsh, Butters, Hughes, Mohs, & Heyman, 1991). Memory in Alzheimer's disease has been studied from several theoretical perspectives based on the following models of memory: structural (Atkinson & Shiffrin, 1968), levels-of processing (Craik & Lockhart, 1972), and episodic, procedural, and semantic (Tulving, 1972). Common to these models is the

notion of dual but interrelated memory components: short-term and long-term memory. In addition to the general decline of memory typical of aging, Alzheimer's patients exhibit unique deficits affecting both of these components. In the earlier stages of the disease, these deficits may appear in either area of memory alone or in both (Becker, 1988). As the disease progresses, memory decrements are seen on a global level. This section will present a brief overview of the impact of Alzheimer's disease on the memory components utilized during medication administration.

Prospective memory. The Craik and Lockhart (1972) model of memory is described in terms of processes and their interactions and that performance is a joint function of environmental and internal factors. The internal factors include the amount of general processing resources available and depth of processing, characterized along a continuum from "shallow" to "deep". The goal of remembering is to recapitulate some previous state, and remembering is facilitated when the same contextual cues present during encoding are available as references during retrieval. The author uses this theory to explain why measures of recall are significantly lower than measures of recognition in the general population and particularly in the elderly. He states that recall of previously presented information is much more difficult than recognition of the same information because it is more reliant on internally generated memory cueing, or "remembering to remember", whereas recognition is cued and supported by environmental markers (Craik, 1986). The self-initiated activities used during recall may be described as retrieval or

reconstructive processes, implying the act of remembering to be voluntary, intentional, and effortful.

Einstein, Holland, McDaniel, and Guynn (1992) leveraged the Craik model for the cognitive operation known as prospective memory. They argued that there are two forms of prospective memory, event-based and time-based. As in the Craik model, an external event is more likely to generate a memory trace than an internal “cognitive survey”. In a study depicting a habitual memory task, Einstein, McDaniel, Smith, and Shaw (1998) found that subjects remembered to perform the desired action approximately 70% of the time.

Huppert and Beardsall (1993) showed in 3 different tasks that prospective memory was significantly impaired in very mild Alzheimer’s disease. The amount of impairment ranged from 28% to 77% of normal scores across different prospective memory tasks and different delay rates between instruction and testing. In a prospective memory task similar to remembering to take a medication (remembering an appointment after a 20 minute delay), the very mild Alzheimer’s disease subjects performed at a level that was only 33% of the normal group’s score for that test.

Episodic memory. Episodic memory impairment is one of the most salient deficits in Alzheimer’s disease, present at the earliest stages (Morris, 1992). The impairment can be separated into long and short-term aspects. Long-term impairment is more obvious behaviorally, with the patient increasingly unable to take in new information and maintain temporal and spatial orientation. Deficits in short-term memory are more subtle

behaviorally, but can be as debilitating to everyday activities. For example, patients can have trouble keeping track of conversations involving several people, and attending to more than one thing at a time.

Retrieval is done best in response to retrieval cues such as, "what is your name?" Retrieval that requires the person's work at finding answers is referred to as "active retrieval" or "recollection." The answer to "what was your second grade teacher's name?" requires an act of active retrieval and is especially difficult for people diagnosed with Alzheimer's disease. These patients can read single words aloud using their printed forms as cues. They cannot, however, retrieve information that requires the generation of retrieval cues as to produce as many answers as possible. For example, they would have difficulty listing many words beginning with a particular letter or sequencing activities from the time they wake up to the time they leave their house.

Batchelder, Chosak-Reiter, Shankle, and Dick (1997), in a modeling analysis of clinical data gathered by Welsh et al. (1991) estimated that healthy elderly adults had an 88% success rate for a test of episodic memory. They estimated that very mild Alzheimer's patients had a 65% success rate for the same information.

Semantic recall memory. AD patients at stage 3-4 retain approximately 20% of verbally presented information after a 10 minute delay, as opposed to 70% for age and education matched controls (Bieliauskas, Fastenau, Lacy, & Roper, 1997; Larrabee, Youngjohn, Sudilovsky, & Crook III, 1993). Storage of information into the long-term memory involves three steps: encoding, storage, and retrieval. Encoding refers

to the process by which new information is interrelated with the existing information. Once information is properly encoded it will be stored in the long-term memory so it can be retrieved in future. Insufficient encoding leads to problematic retrieval of information, which is common among Alzheimer's patients.

Semantic recognition memory. Hart, Kwentus, Harkins, and Taylor (1988) found that normal individuals recalled approximately 80% of visual (pictures) information presented to them when tested for recognition after a 30 minute delay. Under the same conditions, he found that very mild Alzheimer's patients had a recall rate of 45%. These recognition rates remained stable for several days after the initial exposure for both groups.

Working memory decay. One approach to the study of memory, and also to the description of changes in memory caused by age or dementia, has been structural; the notion that memory can be understood in terms of discrete structures and mechanisms (Atkinson & Shiffrin, 1968). These have been presumed to include structures and mechanisms for sensory, primary or working memory, and secondary or long-term memory. Sensory memory captures raw external stimuli (sound, visual, tactile) and has extremely rapid decay rates, measured in tens and hundreds of milliseconds. Baddely and Hitch's (1974) model of working memory consists of three primary components: a central executive processor responsible for initiation and coordination of mental processes, and two storage subsystems of limited capacity, the phonological or articulatory loop (a

repository for verbally encoded items) and the visiospatial scratchpad (a repository for visiospatial items). Each storage subsystem is posited to have its own rehearsal mechanism that updates or refreshes newly encoded memory traces for approximately 30 seconds or less. Card et al. (1983) later defined this time period as ranging from 73-223 seconds for one “chunk” of information. During that process, the item either decays out of the memory store or is encoded into secondary memory. Atkinson and Shiffrin proposed that material encoded into long-term memory is encoded semantically, in terms of its meaning. Effective encoding is dependent on rehearsal of information during its stay in working memory. In this view, inability to encode information into long-term memory will be related to inefficiencies in rehearsal during short-term memory.

Morris and Baddely (1988) propose that Alzheimer’s disease reduces the efficiency of the central executive processor, and that this serves to explain the consistent performance degradation AD patients exhibit on two classic measures of working memory: memory span and tasks involving divided attention. Memory span measures immediate recall of a serially presented string of items: usually digits, words or letters. The tasks of divided attention are variations on the tests developed by Peterson and Peterson (1959), in which a subject is presented with three verbal items to be remembered after a delay, during which the patient is distracted by a subsidiary task such as adding pairs of digits. In addition, the degree of impairment in tasks of divided attention appears to be related to the severity of dementia (Corkin, 1982).

Baddely (1986) argues that a few items can be retained more or less automatically in the previously described storage subsystems, but as storage capacity is approached, the

CES becomes more heavily involved, either coordinating additional cognitive processes such as rehearsal that enable the information to be retained or perhaps acting as a supplemental storage system. An impairment to the CES would then explain memory span decrements in which the capacity of the storage subsystem is approached. However, Cherry, Buckwalter, and Henderson (1996) used backward span procedures to more granularly parse testing of the CES and storage subsystems and have shown that in addition to CES decrements, Alzheimer's patients also exhibit decreased capacity in both storage subsystems.

Tasks of divided attention such as those that would occur if an extraneous event "interrupted" the medication administration task flow are presumed to place demands on the CES component of working memory since they involve sequencing and coordination of mental activity. Placing two demanding tasks together is thought to exceed the processing capacity of an AD-affected CES, resulting in mutual interference between the tasks and a subsequent performance degradation. However, as in memory span tests, it is possible that decrements in the storage subsystems contribute to this effect. The result of this from a performance perspective is a shorter "half-life" for data held in working memory. Research by Hart et al. (1988) showed a 40% decrement (compared to controls) in rate of forgetting for unrehearsed data in very mild Alzheimer's patients over a period of 10 minutes.

Procedural memory. Procedural memory (Tulving, 1972) is acquired implicitly, and is not mediated by conscious recollection. Several studies have found that procedural

learning and retention was not affected by mild Alzheimer's disease (Knopman, 1991; Dick et al., 1996; Eslinger & Damasio, 1986; Bondi & Kaszniak, 1990). The implication of these findings is that certain behaviors (such as placing a pill in one's mouth, taking a drink of water, and swallowing) related to regimen administration remain robust in Alzheimer's patients. The ability to perform the motor skills inherent in medication administration was confirmed by direct observation and multiple interviews with caregivers.

Working memory stimulus discrimination. Allen, Namazi, Patterson, Crozier, and Groth (1992) conducted a study on the impact of Alzheimer's disease on levels of neural noise for letter matching. In a self-paced task, subjects were asked to state if two letters shown on a CRT were the same or different. They found that the percentage of Type I and Type II errors was significantly greater for the very mild Alzheimer's group than for the healthy elderly control group. We assert that this activity is similar to the verification of a correct dose amount by individuals who are administering medication.

SUMMARY

Noncompliance is the dominant factor in medication regimen problems, and often results in hospitalization or institutionalization. Poor recall and use of numerous medications and doses are the primary contributors to unintentional noncompliance.

Alzheimer's disease produces acquired cognitive deficits that eventually block an individual's ability to remain autonomous. These deficits typically damage functioning in a number of perceptual, cognitive, and physical dimensions.

A system that enables early-stage AD patients to be autonomous has potentially significant economic, emotional, and lifestyle benefits for the patients, their families, and society in general. A key feature that enables autonomy is the ability to successfully manage a medication regimen. Unfortunately, there seem to be no clinical studies of medication regimen compliance rates in individuals with very mild to mild Alzheimer's disease. This is understandable given the logistical difficulties of conducting such research. This study attempts to create a simulation model of regimen compliance for normal and AD individuals with the intention of generating predictive data. The data generated by the simulation and the structure of the model itself will be used to make recommendations to address the feasibility of strategies that enable an individual with AD to self-administer a medication regimen.

Augmentation or rehabilitation of cognitive deficits such as those caused by Alzheimer's disease has lagged behind augmentation and rehabilitation for physical deficits (Cole & Dehdashti, 1998). Current approaches to AD have focused on therapies,

rather than prosthesis designed to supplement abilities and thus enable autonomy. The intention of this study is to provide a tool that can be used in the development and evaluation of augmentative systems for individuals in the early stages of Alzheimer's disease progression.

SIMULATION MODELS METHOD

Goals of the Simulation Models. The primary goal of the simulation models is to predict the effects of very mild Alzheimer's Disease (Reisberg and associates stage 3) on the ability to comply with self-administered medication regimens of one and three dose intervals per day. A secondary goal is to use the data generated by the simulations to make recommendations for possible augmentative systems designed to improve compliance.

Scope of Simulation Models. The first two simulation models attempt to replicate clinical performance for both a once and three doses per day regimen for healthy elderly individuals. They include representations of multiple cognitive processes that are germane to administration of medication. The models are representative of population norms for the cognitive processes; they do not represent individual differences. The models represent a targeted portion of the total process of administration of a medication regimen: behavior after the medication has been procured and brought home. To enhance ecological validity, the models also contain stochastic processes that represent real world events external to the subject such as interruptions.

The second two simulation models attempt to predict the performance of stage 3 Alzheimer's individuals for the same regimens. The task structure, cognitive processes, and stochastic processes are the same as those used in the healthy elderly models, though the likelihood of correctly performing cognitive operations is manipulated for each

cognitive parameter to reflect the specific impairments of Alzheimer's disease typical of this stage of disease progression. As in the previous models, the Alzheimer's models are representative of population norms for the cognitive processes; they do not represent individual differences.

Assumptions of the Simulation Model. The major assumption made in both models is that noncompliance in the group of subjects represented is unintentional. The models represent a population that is highly motivated to comply with the medication regimens. The rationale for this is that the same assumption was applied by the authors of the clinical studies that the model was compared against.

The second assumption is that physical limitations such as poor eyesight, immobility, and poor manual dexterity are not contributing factors to noncompliance behavior in either the clinical data or the simulation models. While this assumption could certainly be challenged, there is a lack of clinical data that ties observable behaviors linked to physical limitations to noncompliance behavior itself. Issac et al. (1993) found that degraded motor function was associated with reduced ability to cut pills and open child-proof containers, though their study did not measure how often those activities contributed to noncompliance or if standard medication containers were easier to open and could alleviate the problem.

The third assumption is that the instructions for taking the medication and purposes of the medication are not so complex as to become a factor contributing to noncompliance. This is reasonable given that the studies that were used for model

comparison and validation had relatively simple instructions (e.g., one tablet with food once a day) and used medications familiar to the populations being studied.

The fourth assumption is that certain sets of activities depicted in the models rely on robust procedural schema that are essentially automatic and uninterruptable for both the healthy elderly and Alzheimer's populations. For instance, the act of placing a pill in one's mouth, picking up a glass of water, taking a drink, swallowing the pill, and putting down the glass of water does not require active cognitive supervision. The robustness of this particular schema was observed by this researcher in Alzheimer's patients in the middle to late stages of disease progression at multiple care facilities on multiple occasions.

The fifth assumption is that random events will occur during medication administration that might cause an individual to temporarily disengage from the activity of medication administration. For example, a visitor could knock on the front door or the telephone could ring. The likelihood of successfully returning to the prior activity will be a function of the time away from the activity and the cognitive capability of the group being simulated.

The sixth and final assumption is that the process used by individuals when taking medications is relatively linear and inflexible. Much of the linearity is necessary for logical consistency; it is unlikely that a person would remove a pill from a medication container without first remembering that they need to take a medication and that they had not yet taken that medication. The flip side of this is that differences in compliance strategies across individuals are not possible. For example, the model does not represent

an individual choosing to remove a dose from a container with the intention to take it later, which could be a clinically unobservable factor influencing regimen compliance. The relative inflexibility of the model is a concession to simplicity, and could be re-examined in future models.

Method of Data Collection and its Difficulties. Generalization from neuropsychological test data to actual behavior has been a longstanding challenge for researchers. The sample performance means generated by these tests are point estimates of the true population mean, and are almost certain to deviate from that desired value. By calculating a confidence interval for the value of each different test measure, upper and lower bounds are established on either side of the sample mean, with a specified probability of including the parameter being estimated. Manipulation of a point value within the range of values provided by this calculation provided a method of calibration when the values were inserted into the model. Ninety-five percent confidence intervals were calculated for the data used in this study, leaving a five percent possibility that the interval did not contain the true population mean. The values were expressed in the model as parameters, which allowed probabilistic or deterministic transitions between tasks.

Finding studies that provided clinically controlled data for the specific cognitive operations that exist in medication administration was not difficult. However, the ecological validity of this data within the context of any specific set of activities (such as medication administration) is certainly suspect. Efforts were made to leverage data from

studies that approximated the context of the cognitive activities necessary for medication administration. The use of the data set chosen is not meant to imply that it is unassailable as far as representing population means; it is a best effort at creating a *reasonable* baseline of performance.

Assumptions About Data Used in Simulation. An assumption made in both models is the existence of subject bias to take a medication or not given some uncertainty about whether they had taken it for the prescribed dose interval. This bias is a component of the decision structure representing episodic memory, where the model posits that an individual can either correctly remember an event with assurance, incorrectly remember an event with assurance, or have an uncertain memory for an event. In the case of the one dose per day regimen, the bias is expressed as a tendency (.70 take-.30 not take) to take a medication given an uncertain memory for previous behavior. In the three doses per day regimen, the bias is reversed (.30 take-.70 not take) for the second and third dose intervals to take the medication given an uncertain memory. This reversal of bias is not based on clinically derived data for episodic memory; it is intended to reflect a selection mechanism implied by the data of multiple studies that show substantially higher errors of commission for doses taken earlier in the day than doses taken later in the day (Paes, et al., 1997; Kruse, Rampmaier, Ullrich, & Weber, 1994).

The second assumption is the prospective memory cycle rate. This is based on research by Einstein and colleagues which suggests different probabilities for success on event-

based and internally generated prospective memory. By increasing the prospective memory cycle rate, more chances to recall are created during a given time period.

The Data Used in the Models. Differences in the capabilities of individuals with Alzheimer's Disease of approximately stage 3 are represented with lower probabilities of success/higher probabilities of error and different working memory decay rates. The values of the parameters representing the Alzheimer's population can be seen as cognitive degradation vectors, which could be further elaborated with additional data representing later stages of the disease.

	Healthy Elderly		Very Mild AD	
	Clinical Mean	95% CI	Model Value	Model Value
1. Prospective Memory	.70 per event	.61-.79	.028 per cycle	.01 per cycle
2. Episodic Memory	.88	.80-.96	.92	.65
3. Semantic Recall	.70	.72-.88	.70	.20
Memory				
4. Semantic	.80	N/A	.80	.45
Recognition Memory				
5. WM Decay rate	73-223 sec. for 1 chunk	N/A	73 sec. (Rehearsal)	45 sec. (No Rehearse)
6. WM Type I Error	.029	.015-.043	.029	.196
7. WM Type II Error	.027	.014-.04	.027	.13

Table 1. Mean Scores (SD) and 95% Confidence Intervals for the data used for model parameter generation.

The value for prospective memory (normal) was based on research by Einstein et al. (1998). The value for prospective memory (AD) was based on the previously referred to research as well as research by Huppert and Beardsall (1993). The prospective memory rate per cycle was created by dividing the event-based rate of 0.79 (the high end of the 95% CI for the sample mean) by the estimated number of time-based recall chances (23) an individual would have during a typical waking day. The number of chances was derived from a 12 hour waking day with 30 minute “background” activities between each memory opportunity. This time was chosen because it represents a naturalistic span dedicated to a particular activity, such as eating a meal, watching a television program, reading a newspaper, or washing laundry or dishes.

The values for both normal and very mild Alzheimer’s episodic memory were based on research by Batchelder et al. (1997). The values for recognition memory were based on research by Backman and Herlitz (1990). The value for normal working memory decay rate was taken from research by Card et al. (1983). The value for the Alzheimer’s working memory decay rate was based on the Card et al. (1983) study and research by Hart et al. (1988). Finally, the values for working memory type I and II errors were based on research by Allen et al. (1992).

The model was calibrated by accelerating or decelerating the prospective memory cycle time during an event. It was also calibrated by the “bias” embedded in uncertain episodic memory performance.

Limitations of the Simulation Model. The models do not attempt to explain the processes or structures underlying cognition, they merely assert that performance across these structures or processes is different. The models do not account for possible correlation between cognitive operations. Temporary changes of location (an individual goes out for lunch) that could be an unmeasured contributing factor in regimen noncompliance are not represented, due to the lack of data available from clinical studies.

Process Flow Chart and Structure of Simulation Models. The following illustrations depict both the high-level process flow of the model and the model structure created to simulate the process. The rectangular boxes represent tasks or groups of operations and while relatively arbitrarily bounded, are useful in communicating process flow. The oval boxes represent distinctive atomic operations of the system while the diamond shapes represent decision logic that determines the possibilities of transition to the next operation or operations. The lines connecting the tasks or activities and decision logic are directional and show input and output paths for each entity. The task networks were comprised of activities relevant to medication administration and transitions between activities that were both probability and rule-based, depending on the type of parameter being represented. The diamond-shaped decision nodes are labeled with a “T” (tactical), “P” (probabilistic), or “PT” (tactical and probabilistic) to note the type of decision logic used.

When the model starts, a “tag” is launched from the start box towards the task network. The movements of the tag are limited by the paths available to it, the times it

spends in an activity, and the routing of the decision nodes. A task must be successfully completed in order to proceed to the next task. If the task is not successfully completed, the tag returns to the initial activity of task 1.0 (prospective memory). Figure 1 describes the overall process for the one dose per day regimen. Figure 2 describes the overall process for the three doses per day regimen.

Figure 1. Task network for a 1 dose per day regimen.

Figure 2. Task network for the 3 doses per day regimen.

The structure of the three doses per day regimen is essentially the same as the one dose per day regimen, with the difference being two additional replications of the prospective memory task group. They represent the same processes as the first

prospective memory task group, but for the afternoon and evening time periods. The routing between the tasks for the three doses per day regimen also reflects this and directs tags to the appropriate prospective memory task group pending the time of day.

Figure 3 describes the activities grouped together as “prospective memory” for the one dose per day regimen. The parameters represented in this task group are prospective memory (#1) and episodic memory (#2). The large triangles at the top and bottom of the page show where a tag has come from or can go to. The numbered shaded areas correspond to the parameters listed in table 1 on page 42. Activity 1.1 represents the background activities the simulated subject is engaged by throughout the day. The activity has a duration of 30 minutes, at which point the tag is released to the first decision node. If the tag has passed through activity 1.1 one time only (for the 3x/day regimen, this statement also includes activity 2.1 and 3.1), the decision node labeled “T” (tactical) routes it to activity 1.2, “event-initiated prospective memory”. This activity represents the potential activation of prospective memory for taking a medication that is facilitated by an event. In the case of the one dose per day model, this activity can be thought of as breakfast. In the case of the 3x/day dose interval, it can be breakfast, lunch, or dinner. Given a prospective attention clock speed of 1x/minute during a meal and an activity duration of 30 minutes, the tag has up to 30 chances each at a probability of .028 (normal) or .016 (AD) to move on to activity 1.3, “disengage”. If the tag does not do this, then it is routed to activity 1.15, “delay dose” and then back to activity 1.1.

If the tag has passed through activity 1.1 between 2 and 24 times (in the 3x/day regimen, the equivalent is activity 1.1, 2.1, or 3.1 between 2 and 8 times), it is routed to

activity 1.13, “time-base prospective memory”. Once again, this is because the simulation is representing 12 hours of continuous conscious behavior and a mean “background activity” time of 30 minutes. Thus, 0.5 hours per background activity X 12 hours consciousness - 1 event = 23 possible opportunities for prospective memory attention in the 1x/day regimen. This activity represents the possible activation of prospective memory for taking a medication that is internally generated by the subject. The tag has the same probability of moving on to activity 1.3 as was the case in 1.2. However, it only has one chance of doing so. If it does not, it is routed to activity 1.15, “Delay Dose” and then back to activity 1.1.

If the tag has passed through activity 1.1 more than 24 times, it is routed to activity 1.14, “End of Day”. At this point, the tag is routed to one of four “collection” boxes depending on its previous behavior (Compliant, omission, commission, or 2x commission).

Activity 1.3 represents a subject’s ability to disengage from a stimulus competing with the intention of taking medication. In both the healthy elderly and AD models, the probability of successfully disengaging was 1.0. As more research is conducted on absolute ability to disengage from a stimulus, this point in the model can be modified.

Activity 1.4, “episodic memory” represents a subject’s ability to remember whether or not they have taken the medication for the dosage period they are in. Depending on whether or not the tag has passed through the activity associated with successfully taking a medication, it is routed to either activity 1.5, “Not Taken”, or activity 1.9, “Taken”. In either case, the tag then has a 0.92 probability (0.65 for AD) of

being routed to “take med”, a 0.04 probability (0.175 for AD) of being routed to “unsure”, and a 0.04 probability (0.175 for AD) of being routed to either “take” or “no take”, depending on which branch of the network the tag is in. These probabilistic transitions represent three possible memory states: having a correct memory, an incorrect memory, and an unsure memory. The transitional probabilities from the two “unsure” activity nodes reflect different biases depending on the number of dose intervals per day. In the 1x/day model, if the subject has not yet taken the medication, we assert that they will have a bias of 0.70 to take the medication and a bias of 0.30 not to take the medication. This bias is reversed in the 3x/day model. The proportions of this bias were used to calibrate the performance of the model.

Figure 4 describes the activities grouped together as “go to medication”. The parameters represented in this task group are semantic recall memory (#3) and working memory decay rate (#5). Once the simulated subject has correctly or incorrectly decided to go forward in the administration process, the tag arrives at activity 2.1, memory for medication location. The tag then has a probability of 0.8 of being routed to activity 2.2, “yes-correct”, a probability of 0.1 of being routed to activity 2.6, “yes-incorrect”, and a 0.1 probability of being routed to activity 2.7, “no”. The structure is analogous to the one used for episodic memory earlier in the task network model, though it represents a different memory structure (semantic recall). If the tag is routed to 2.2, it represents a correct recall of medication location; it then proceeds to activity 2.3, “go to medication location”. If the tag goes to activity 2.6, it represents an incorrect memory of location. The tag then goes to activity 2.8, “go to wrong location”. This activity has a mean time

Figure 3. Activities and decision processes for the “prospective memory” task.

of 20 seconds, at which point the tag goes to activity 2.9, “search”. The tag also winds up at the “search” activity if there is no memory for the medication location. The “search” activity has a mean time of 30 seconds with a standard deviation of 15 seconds. These values were not empirically derived; they represent an a-priori attempt to quantify the possible time spans of this activity.

At this point, the first stochastic event of the model can occur. From both activity 2.9 and activity 2.3, there is a 0.05 probability that a spontaneous event will occur that will interrupt the administration process. An example of this would be a phone call or knock on the door. The interruption has a mean time of 120 seconds with a standard deviation of 60 seconds. During the interruption, it is assumed that the subject is not actively rehearsing the intention to complete the regimen, rendering that intention vulnerable to the working memory decay rate for the simulated population. When the interruption ends, a probability is dynamically calculated that determines transition probabilities to three possible activities given the strength of the residual intention. If the residual intention has degraded 25%, there is a 0.75 probability that the tag will continue to activity 2.5, “find medication”. The remaining 0.25 is split equally between the probabilities of returning to activity 2.1 “Loc. Mem” and 1.1. These two paths represent a subject either starting over at the beginning of the task group or completely forgetting and returning to the background activity. They are essentially memory failures of differing severity.

Figure 4. Activities and decision processes for the “go to meds” task.

Figure 5 describes the activities grouped together as “acquire meds”. The parameters represented in this task group are semantic recognition memory (#4), working memory decay rate (#5), and working memory type I (#6) and type II (#7) signal verification errors. There is also another possible instance of a random interruption, which functions as before.

Figure 5. Activities and decision processes for the “acquire meds” task.

Figure 6 describes the activities grouped together as “administer meds”. The parameters represented in this task group are working memory type I and type II signal verification errors. The majority of the activities that make up this task group are schema-based procedural activities, and will exhibit robust performance despite the presence of Alzheimer’s disease. While reading certainly demands conscious processing, we assert that the instructions for the regimen being simulated are simple enough not to cause any performance degradation in either the healthy elderly or the Alzheimer’s individuals. The two areas of interest are the decision nodes after activities 4.6 and 4.7. At this time, a subject has acquired either the correct number of pills (1) or too many pills (>1). Since it is reasonable to assume that many people “dump” some pills out of the container into their hand, we have chosen a 0.50 probability that they will get one pill and a 0.50 probability that they will get more than one pill. If they have one pill, they either correctly verify that they only need one pill, or they commit a type I error and think they need more pills. Likewise, if they have >1 pill, they either correctly verify that they need to put a pill or pills back, or they commit a type II error and take more than one pill. The type II error leads directly to the next activity and it is assumed that more than one pill will be taken for that dose event. The type I error loops back into the verification procedure, which happens again. We assert that the verification procedures do not affect one another; they are autonomous cognitive events.

Figure 6. Activities and decision processes for the “administer meds” task.

Model Runs. A 2 X 2 factorial experiment was run with 20 replicates of 5 sets of 100 runs for each factor-level combination. The factors manipulated were cognitive status (normal elderly and Alzheimer's elderly) and dose events (one dose per day and three doses per day).

Performance Measurements. The performance measurements for the one dose per day models were regimen compliance, errors of omission, errors of commission, and pill count. The three doses per day models tracked the same performance measurements for each simulated day of behavior, and in addition tracked errors of omission and commission for each dose event.

Verification, Validation, and Output Analysis

Method of Verification. Verification deals with the model itself; whether it performs as intended by the simulation programmer. It is essentially a debugging process of the simulation model. Because of the relatively complex nature of the models constructed for this study, it was important to verify the models by simulating the ideal situation: 100% regimen and pill count compliance with no time deviation from the required dose events. To do this, the parameters that represent cognitive performance were assigned probabilities of 1.0, reflecting "perfect" cognitive performance within the context of the model. The result of the ideal situation simulations for the one dose per day

and three doses per day models was as expected: all runs exhibited 100% regimen and pill count compliance and no deviations from the prescribed dose intervals.

Output Analysis and Method of Validation. Validation concerns whether the model is simulating the real system it is based on. One of the most frequently used techniques for validation is to compare output from the model with clinical observations of the real system and determine statistical differences between them. If the model is a valid representation of the real system, there should be no statistical differences between the two. As the number of data points compared between the real and simulated systems increases, so does the confidence with which one can assert model validity.

The results from the models representing a healthy elderly population were compared primarily with data from the Paes et al. (1997) study. This study was chosen because it focused on a healthy elderly population (mean age 69.2, SD 10.9) who administered their medications without assistance from either another individual or a special pill container/organizer, had a larger number of subjects than comparable studies (n for 1 dose per day=40, n for 3 doses per day=15), used state of the art (MEMS) data collection electronics, and isolated one element contributing to regimen complexity: number of dose events per day. Additional informal comparisons were made with the Eisen et al. (1990), Kruse and Weber (1990), Cramer et al. (1989), Kruse et al. (1994), and Bothelo and Dudrak (1992) studies.

		1x/Day		3x/Day	
		Mean Score	95% CI	Mean Score	95% CI
Healthy	Regimen	79.1 (18.8)	73.2-85.0	38.1 (35.9)	21.2-55.0
Elderly	Compliance%				
	Pill Count%	98.7 (18.6)	92.8-104.7	65.8 (30.1)	49.1-83.5

Table 2. Mean Scores (SD) and CI for regimen compliance and pill count in a healthy elderly population (Paes et al., 1997).

SIMULATION MODELS RESULTS

		1x/Day		3x/Day	
		Mean Score	95% CI	Mean Score	95% CI
Healthy	Regimen	79.6 (1.7)	78.8-80.4	42.5 (3.0)	41.1-43.9
Elderly	Compliance%				
	Omission%	14.2 (1.2)	13.6-14.8	52.1 (3.0)	50.7-53.5
	Commission%	6.2 (1.3)	5.6-6.8	3.2 (0.7)	2.9-3.5
	Pill Count%	94.1 (1.8)	93.3-94.9	81.5 (2.7)	80.2-82.8
Very Mild	Regimen	44.4 (2.2)	43.4-45.4	5.6 (0.6)	5.3-5.9
AD	Compliance%				
	Omission%	50.9 (2.3)	49.8-52.0	90.3 (5.2)	87.9-92.7
	Commission%	4.7 (0.7)	4.4-5.0	4.1 (0.9)	3.7-4.5
	Pill Count	59.2 (1.3)	58.9-60.5	40.8 (4.0)	38.9-42.7

Table 3. Simulated mean scores (SD) and CI for regimen compliance omissions, commissions, and pill count in healthy elderly and Alzheimer's Disease populations.

Validation. The data generated by the simulation models for the healthy elderly population were compared to the clinical data of the Paes et al. (1997) study. Since we did not have access to the original data collected in that study and were uncertain as to the normality of the data, no statistical comparisons were made. Despite that limitation, it

was clear that the model did generate data that was consistent with the data gathered by Paes and his colleagues. The following figure compares the mean scores and confidence intervals of regimen compliance for the 1x/day and 3x/day dose intervals for both sets of data.

Figure 7. Comparison of regimen compliance mean scores and 95% CI's between the Paes et al. (1997) study and the simulation data generated by this study.

As shown in the preceding figure, the mean score of the simulation data at the 1x/day dose interval is almost exactly the same as the clinical data. For the 3x/day dose interval, the difference is slightly larger but still falls near the center of the confidence interval. The simulation data for regimen compliance is also close to the clinical data reported by Cramer et al. (1989), Eisen et al. (1990), and Botelho and Dudrak (1992). While this comparison shows the possibility that the data generated by the simulation and the clinical data are representative of the same underlying population, it is premature to state that the data sets are likely to come from the same population. However, additional comparisons can be made that strengthen this case.

Paes et al. (1997) found that on average, subjects committed errors of commission on 4.9% of the days tracked by their study. This percentage reflects the combined performance of the subjects in the 1x/day and 3x/day conditions. Eisen et al. (1990) found an overall commission rate of 4.5%. By combining the data generated by the simulation models in the 1x/day and 3x/day conditions, a similar percentage of 4.7% is found. The Paes et al. (1997) study also reported that the percentage of the participants in the study who made commission errors was much higher for the 1x/day dose interval (40%) than for the 3x/day dose interval (13.3%). While these percentages are not directly comparable to the simulation data due to its artificial sample homogeneity, the simulation did produce a substantially larger error rate for the 1x/day dose interval (6.2%) than the 3x/day dose interval (3.2%). The 6.2% commission rate in the 1x/day dose interval was also quite similar to the 7% commission rate reported by the Kruse et al. (1994) study.

Finally, the confidence intervals for pill count in the simulation were within the bounds of the confidence interval for pill count in the clinical data, though the means of the data for both studies were less similar than the means of the regimen compliance data.

Figure 8. Comparison of pill count mean scores and 95% CI's between the Paes et al. (1997) study and the simulation data generated by this study.

Analysis of Variance. Analysis of variance of the data generated by the simulation models was conducted to determine the effects of number of dose intervals per day (1x and 3x) and cognitive status (healthy elderly or very mild Alzheimer's disease) on medication regimen compliance.

Figure 9. Effect of number of dose intervals on healthy elderly and AD populations for the simulation study.

Figure 10. Effect of cognitive status at “once” and “three” times daily dose intervals for the simulation study.

Number of dose intervals per day had a significant effect on regimen compliance ($F(1,76) = 6149.37, p < .0001$), with more dose intervals per day leading to decreased regimen compliance. Cognitive status also had a significant effect on regimen compliance ($F(1,76) = 6796.06, p < .0001$), with presence of very mild Alzheimer’s disease leading

to decreased regimen compliance. No significant interaction was found between number of dose intervals per day and cognitive status ($F(1,76) = 3.68, n.s.$), indicating that presence of the 3x/day regimen combined with Alzheimer's disease did not lead to a greater decrement in regimen compliance than either factor alone.

Magnitude of Effect. An estimation of the magnitude of effect of each treatment condition and the interaction between them was calculated using omega squared. Differences due to number of dose intervals per day accounted for 52.2% of experimental variability. Differences due to the presence of Alzheimer's disease accounted for 47.2% of experimental variability. The remaining variability (0.6%) was due to random error.

SIMULATION MODELS DISCUSSION: EFFECT OF ALZHEIMER'S DISEASE ON REGIMEN COMPLIANCE

As expected, the simulation that represented a very mild Alzheimer's disease group produced significantly lower regimen compliance than the simulation that represented the healthy elderly group. The results suggest that, without external cognitive support, patients with even very mild Alzheimer's disease will be unable to comply with even the simplest medication regimen. It is important to note that this simulation was designed to isolate the effects of Alzheimer's disease on regimen compliance, and in the real world, individuals are likely to use some support. This can be as simple as written reminders in conspicuous locations, setting alarms, and tracking dose administration to prevent commissions. These simple strategies are likely to improve compliance for the Alzheimer's population. However, the sheer number of points during the administration process at which errors could be made and the decreased ability to integrate information from multiple support sources suggests that the Alzheimer's population would benefit less from these simple strategies than a healthy population would.

Given the extremely small variances in the sample means for the simulated data, it is not surprising that no significant interaction was found between the treatment factors. It is suspected that there would be a significant interaction if a heterogeneous population were represented by the model, leading to a larger variance from the sample mean.

GENERAL DISCUSSION

An important aspect of a simulation model is the generalizability of the behavior produced by the model to the real-world situation it represents. This is a substantial undertaking for complex human/system behavior, since the cognitive operations and processes undertaken by a human in the real world are represented by relatively crude theoretical constructs in the model that are unlikely to capture such subtleties as cognitive operation interaction and dependence. Given this inherent complexity, every model will fail to replicate exact behavior to some degree. In addition, using parameter data from studies in which a particular cognitive operation was tested outside the context of medication administration can certainly be debated. Lastly, while any model can be manipulated to produce output completely consistent with the system it simulates, there will always be some uncertainty over whether or not the model is producing the output by the same means as the real system.

Despite these shortcomings, the models created for this study are important and useful in four ways. First, they provide initiative for clinical research specifically targeted at the cognitive operations germane to medication administration. Second, they establish a framework that more accurately targeted, contextually sensitive research data can be “plugged in” to and studied from a systems perspective. Third, they can be used to generate recommendations for strategies designed to augment individual behavior. Fourth, they can be used as evaluation mechanisms for these strategies. These activities contribute to iterative refinement of the models, which in turn generate more refined

targeting of clinical studies. Given this rationale, it is important that these models be viewed as a starting point for an ongoing process rather than a final statement.

Refinement Directions. Because identical parameter values were used for all model runs, the simulated data does not display the same variability as the clinical data it seeks to represent. The subject “profiles” are identical collections of point estimates. This is an important concern given the heterogeneous profiles of Alzheimer’s disease symptoms at the simulated stage of progression. For instance, a single subject could have prospective memory performance similar to that of the healthy elderly population but episodic memory performance much worse than the parameter value chosen for the Alzheimer’s population model. For this reason, recommendations for an augmentative system for Alzheimer’s individuals based purely on estimated population performance means are unlikely to adequately address patients with “atypical” symptom profiles. Two strategies can be used to avoid this shortcoming. First, the recommendations for the augmentative system should present a conservative bias to reflect the possibility that an individual could be performing much worse than the population at any specific cognitive parameter. Second, future iterations of the models should reflect the individual variability of cognitive aptitude across the chosen parameters. To more accurately represent the performance variance seen in a heterogeneous population, the parameters could be converted into distributions that would be randomly sampled as a tag passes through the parameter decision point. By doing this, a unique subject “profile” could be created for each model run.

A second concession to simplicity made by the models is the discreet representation of time. In their current implementation, the models have variable time “chunks” allotted to pre-existing activities, walking to the medication location, searching, and interruptions. The lack of a continuous clock prohibits a more complete representation of sustained cognitive workload.

A final concession is the relatively rigid procedure the model uses to represent the medication administration process. For instance, travelling to different locations is not accounted for. It is also possible that an individual would be taking non-prescription medications in conjunction with a prescription medication, and that this could influence the activity order in some tasks.

Further Application of the Simulation Model. The primary utility of the simulation models is the ability to evaluate multiple augmentative strategies and systems in a relatively short time frame. In the future, we hope to simulate a number of these systems with the intention that the data generated by the simulations will inform the real-world implementation of such systems. In order to do this, additional factors contributing to noncompliance behavior will need to be added to the simulation. The first likely factor would be number of medications taken concurrently; this would not require a substantial redesign of the existing model to simulate. A second factor could be disease progression. The parameter values depicting cognitive operations could degrade over a given time period, allowing development of a dynamic augmentative system that adapts to the patient.

Augmentation Recommendations. The task structure of the models allows for several recommendations for an augmentative strategy. First, patients must be alerted by some external means when it is time to take a medication. This greatly reduces the burden placed on prospective memory. The alert should be unambiguous, and should contain a direct statement such as “take medications now”. However, care must be taken to adapt the alerts not only to the prescribed dose intervals, but also to the daily activity intervals of the patient. For instance, an alarm at 8:00am is likely to be an annoyance if the patient regularly eats breakfast (and takes medications) at 10:00am. A wristwatch-like device that can communicate alerts through multiple sensory channels (sound, sight, and touch) would be one possible solution. In the event that this device is not worn for some reason, another device with a fixed docking area (like a telephone receiver on a base) and high level of visibility (to avoid being misplaced) should provide comparable functionality, though likely without the touch component. The device should be in communication with a pill dispenser (and in the case of the fixed-location device, possibly integrated) that tracks whether or not a pill has been dispensed for a particular dose interval. By doing this, the system provides a safeguard against anything that might derail the process between alert and administration. If the pill is not dispensed within defined time period after an alert has been given, additional alerts can be given until the dose is dispensed. This behavior can also be tracked (with the patient’s permission) to gather information on a patient’s regimen compliance. If the patient needs to take medication when away from the home, the device should be portable. However, this

issue should be examined more closely in subsequent studies because while it affords mobility, it creates an opportunity to misplace the device.

The pill-dispensing device should have individual compartments that can be loaded with only the medications necessary for a particular dose interval in the exact amounts to be taken. This eliminates the need to identify and verify individual medication containers or individual pills. This is especially important for Alzheimer's patients, who are 5-6 times more likely to make type I or II verification errors than normal individuals.

The pill-dispensing device should be able to display the name of and written instructions for each dose, such as "take with food". The instructions should be in a large, easily readable font displayed at a level of luminosity appropriate for low-light conditions. The device should give confirmation that a dose has been dispensed, and this information should be visible until the next dose event is scheduled.

The pill-dispensing device should not have to be loaded by the patient, since this places a cognitive burden of calculation and planning, a physical burden of fine motor coordination, and a visual burden. This recommendation entails that some other person or persons be responsible for loading the device, and has substantial implications on the health care system in general.

CONCLUSIONS

Self-administration of medications by the elderly is an activity that can have significant repercussions if not done correctly. Unfortunately, many opportunities for error exist throughout the procedure, which can compound as a regimen becomes more complex. The presence of very mild Alzheimer's disease is likely to lead to higher error rates and significantly worse compliance if external supports are not available. An integrated system of support is more likely to improve compliance than a series of discreet supports. The models created in this study are a first step needed to support the development of such a system. The models can serve as dynamic testing platforms, allowing many regimen support strategies to be evaluated and refined in advance of prototype development and field studies, resulting in more focused, cost-effective development efforts.

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