Rezulin: how effective and efficient diabetes treatment?

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Abstract: System dynamics simulation is used to assess the dynamic effects of using the new drug «Rezulin» for the intensive treatment of diabetes, a most prevalent disease among patients of the Veterans Integrated Service Network (VISN 3) in the New York City metropolitan area. According to the Brooklyn VA Medical Center data, one in five of its outpatient visits is associated with diabetes and approximately 10,000 of the VISN 3 veterans are diabetic. Although the effects of diabetes on the development and progression of long-term complications have been established, about 90 percent of the VISN 3 diabetic veterans do not seek treatment and thereby create a tremendous cost because of complications. These are mostly type 2 diabetes patients who prefer to defer insulin injection therapy for as long as possible because of the inconvenience, the cost, and the pain of constant blood monitoring and insulin injections. Those who seek treatment, diet, exercise, and use oral drugs or insulin therapy, generally have less costly complications, but there is still a high cost associated with their treatment and, more importantly, they can also become resistant to insulin. Because *Rezulin* directly treats insulin resistance, and it can also lower the HbA1c level of patients (a clinical marker of disease severity assessed via a blood test), this new drug is expected to increase the life time of diabetics by more than 1.5 times. Our model incorporates real-life policy parameters and NIH statistics in order to assess the potential effectiveness and monetary benefits of switching from insulin to the Rezulin oral treatment.

Introduction

Diabetes is a deadly, insidious disease that consumes one out of every seven health-care dollars spent in this country. It affects 16 million Americans, only half of which are officially diagnosed. Among diagnosed patients, insulin-dependent diabetes affects 8 to 10 percent of them, usually under 30 years of age. It is a chronic condition caused by low or no insulin production by the pancreas. In order to survive, patients must self-administer insulin injections once or several times a day.

Among all diagnosed and undiagnosed diabetics, most suffer from type 2 diabetes or adult-onset Non-Insulin Dependent Diabetes Mellitus (NIDDM). The pancreas does produces insulin under this condition but, over time, human cells fail to utilize the body's insulin production to lower blood sugar. They become «insulin resistant». Type 2 diabetes patients can be treated with diet, exercise, drug and sometimes insulin therapy. Most patients prefer to defer insulin-injection therapy as long as possible, however, because of the inconvenience, cost, and pain caused by constant blood monitoring and insulin injections.

Those suffering from diabetes also suffer a serious multitude of long-term complications. Heart disease is probably the biggest killer. The death fraction of middle-aged diabetes patients is twice as high and their heart-disease death fraction two to four times higher than non-diabetic middle-aged persons. Stroke risk is 2.5 times higher for persons with diabetes than for those without, and high blood pressure affects 60 to 65 percent of diabetes patients.

Blindness is another terrible complication. Diabetes is the leading cause of new cases of blindness among adults 20 to 74 years old. Kidney disease is yet another complication, where most diabetics suffer from end-stage renal disease, and thereby must have kidney dialysis and transplantation. Diabetes patients also suffer from mild to severe nerve damage that often leads to amputations. More than half of lower limp amputations are associated with nerve damage caused by diabetes.

In addition to suffering its complications, diabetics suffer financially too because of the costs associated with the disease. First and foremost is the direct medical cost of treating the complications. Second is the indirect cost of disability, work loss, and premature mortality. Diabetes is the fourth leading cause of death by disease.

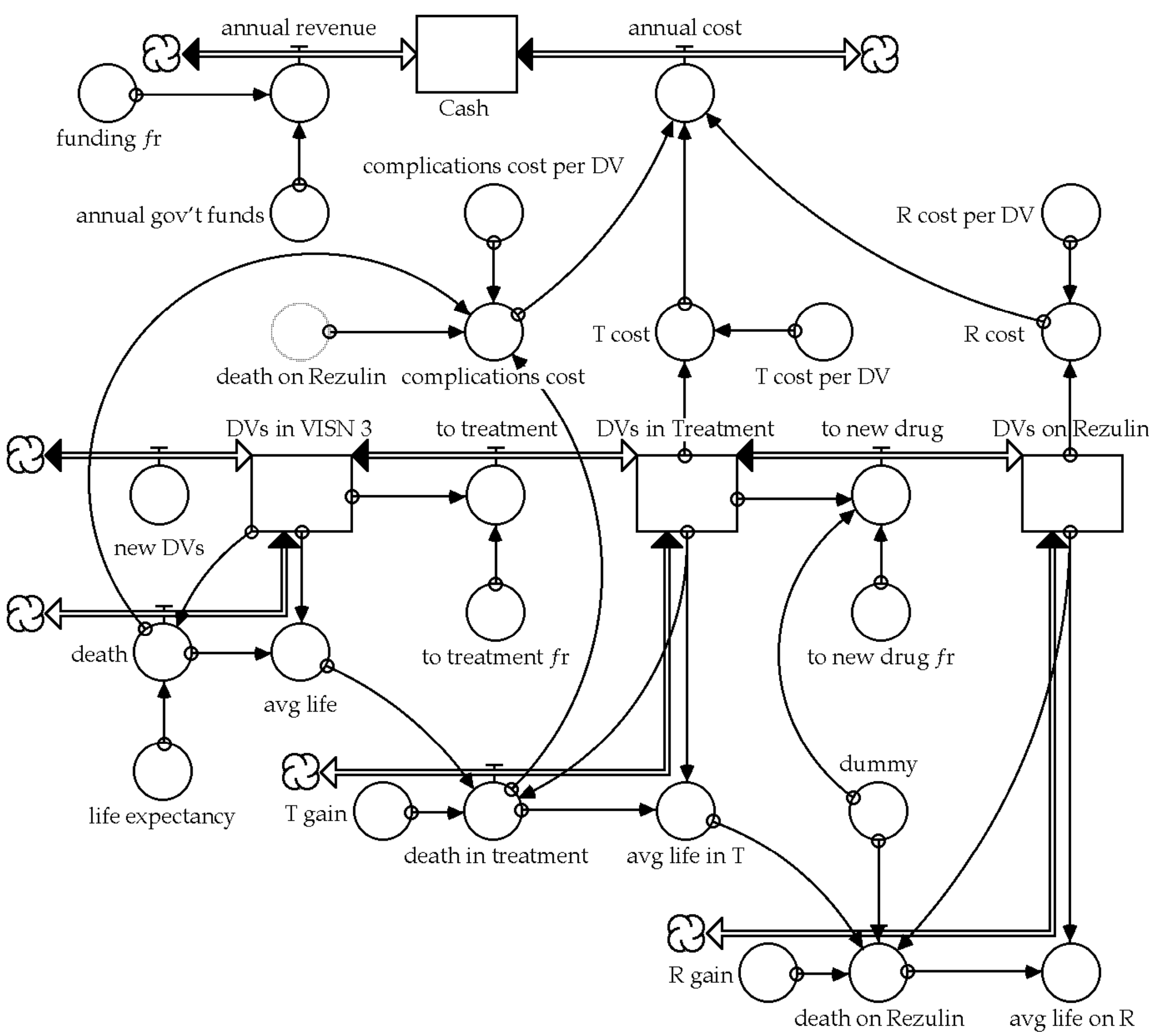
The morbidity, mortality, and cost of diabetes can be greatly reduced, however, if patients undergo treatment. This essay describes a system dynamics simulation model which shows how therapy with a novel new drug called *Rezulin* can profoundly improve the well-being of diabetics. Rezulin is a new oral-antidiabetic drug which works directly on insulin resistance and, thereby gets to the root of the disease process.

Model Description

Specifically, we looked at a patient population where diabetes is a prevalent disease: the Veterans Integrated Service Network (VISN 3) in the

New York City metropolitan area. One in five outpatient visits at VISN 3 is associated with diabetes. Although about 10,000 diabetic veterans belong to VISN 3 (DVs in VISN 3, Fig. 1), because many of them are not in treatment, they pose a tremendous financial burden with a 15-year *life expectancy* (years to death from diagnosis). The diabetic veterans on the other hand who do seek treatment (DVs in Treatment, Fig. 1), diet and exercise counseling, and other drug or insulin therapy experience less costly complications and live longer (T gain, Fig. 1). There is a cost (T cost, Fig. 1), however, to that treatment.

Fig. 1
Veterans Integrated Service Network (VISN 3) diabetes management model



The new drug Rezulin works directly at treating the insulin resistance that human cells develop through time and lowers diabetics' HbA1c level (a clinical marker of disease severity determined via blood test). Therefore, those on Rezulin should live a 1.5 times longer (R gain, Fig. 1). This value (*s.a. Appendix* for model parameters and equations) was derived from the Diabetes Control and Complications Trial (DCCT), which showed that lowering diabetics' blood glucose and HbA1c reduces the microvascular and neuropathic complications risk. Although the trial was performed with type 1 diabetics, medical researchers feel that the results apply to type 2 diabetics too. The model also incorporates government's funding for VISN 3 ($1,009,714,793), with 15 percent ($151,457,218 per NIH) spent on diabetes.

Simulation Results

In order to see what the implications of the VISN 3 situation and data are, we run simulations from zero to twenty years, with a computation interval dt=0.125, using the *Runge-Kutta* 4 integration method. Initializing at steady state produced the results of Fig. 2. Although the number of diabetic veterans (DVs) in VISN 3 remains constant throughout (line #1, Fig. 2a), when the *dummy* variable of Fig. 1 changes from zero to one after year 5, diabetic veterans in treatment migrate (line #2, Fig. 2a), and thereby DVs on Rezulin rise (line #3, Fig. 2a).

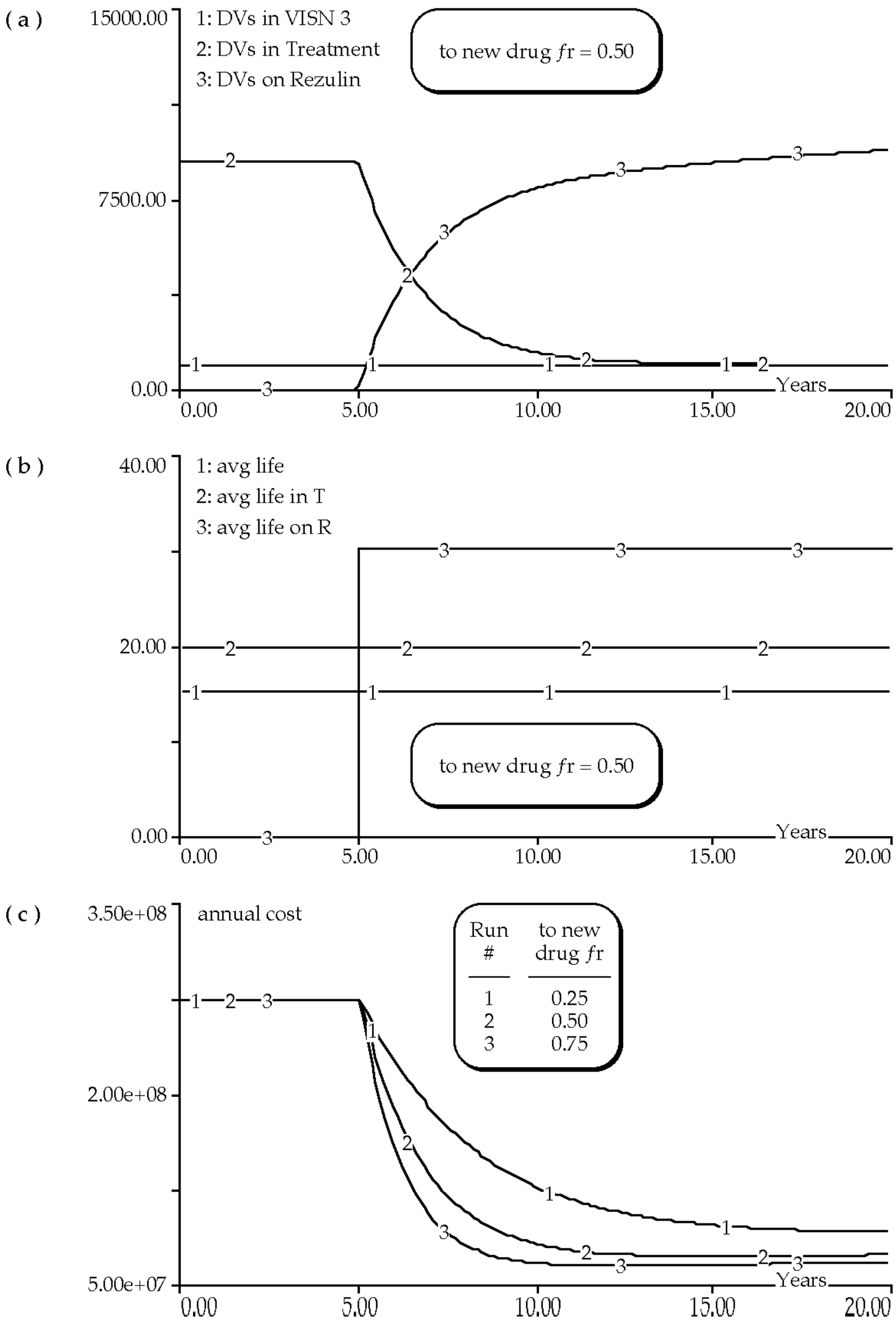
Even in this *ideal* steady-state run, diabetics who seek no treatment die off quickly because of complications (line #1: *avg life*, Fig. 2b), while those in treatment live longer (line #2) and those on Rezulin live the longest (line #3). These morbidity-defying results assume that a *constant* 50 percent of DVs migrate from conventional to Rezulin drug therapy. Figure 2c, however, shows how the annual cost improves markedly when the DV migration fraction (fr) to Rezulin rises from 25 to 50 to 75 percent. The increased life span of diabetic veterans on Rezulin reduces *complications cost*, which in turn causes *annual cost* to decline.

Figure 3 shows the results of a more *pragmatic* current-state system initialization. Again, the Rezulin option does not exist before year 5 (*dummy*=0), so the number of DVs in VISN 3 (line #1, Fig. 3a)) declines as they seek treatment, thereby causing the number of DVs in Treatment to rise (line #2, Fig. 3a). Once Rezulin comes into play after year 5 (*dummy*=1), however, the new drug wins diabetic veterans over (line #3, Fig. 3a), causing the number of those in conventional treatment to decline (line #2,

Fig. 3a). To get a better feel of what might transpire in reality, *life expectancy* is permitted to vary, hence the jagged graphs of Fig. 3. This pragmatic run shows Rezulin to be an effective and efficient diabetes treatment: effective because it extends the *average life* of diabetic veterans (Fig. 3b), and efficient because it lowers the network's *annual cost* (Fig. 3c).

Although the *life expectancy* variability is removed to smooth its graphs, Fig. 4 moves on to a *most pragmatic* run with Rezulin being available now,

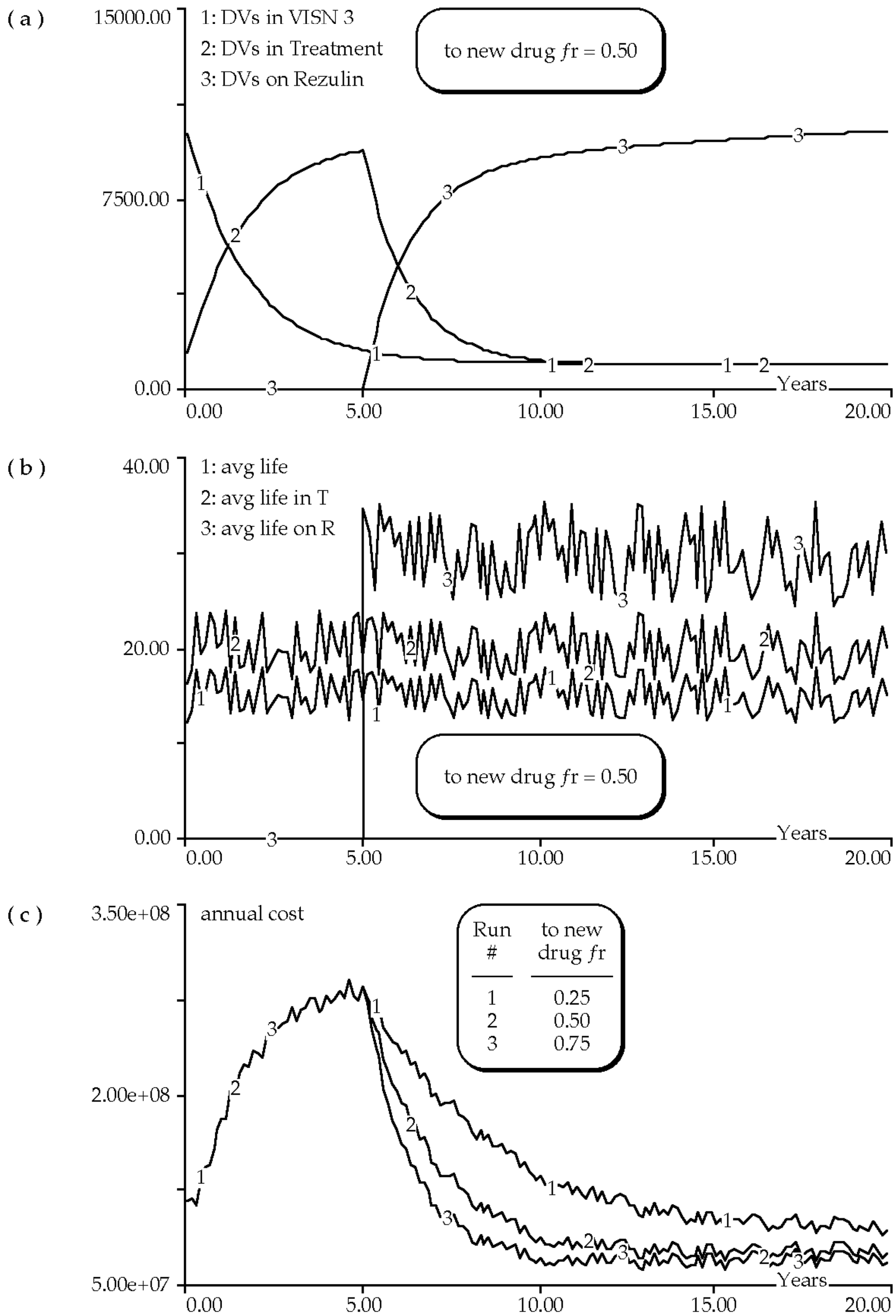
Fig. 2
Simulation output time-series graphs with steady-state initialization



at t=0, not 5 years from now. As diabetic veterans who seek no treatment (line #1, Fig. 4a) begin to do so, and those in treatment migrate to Rezulin

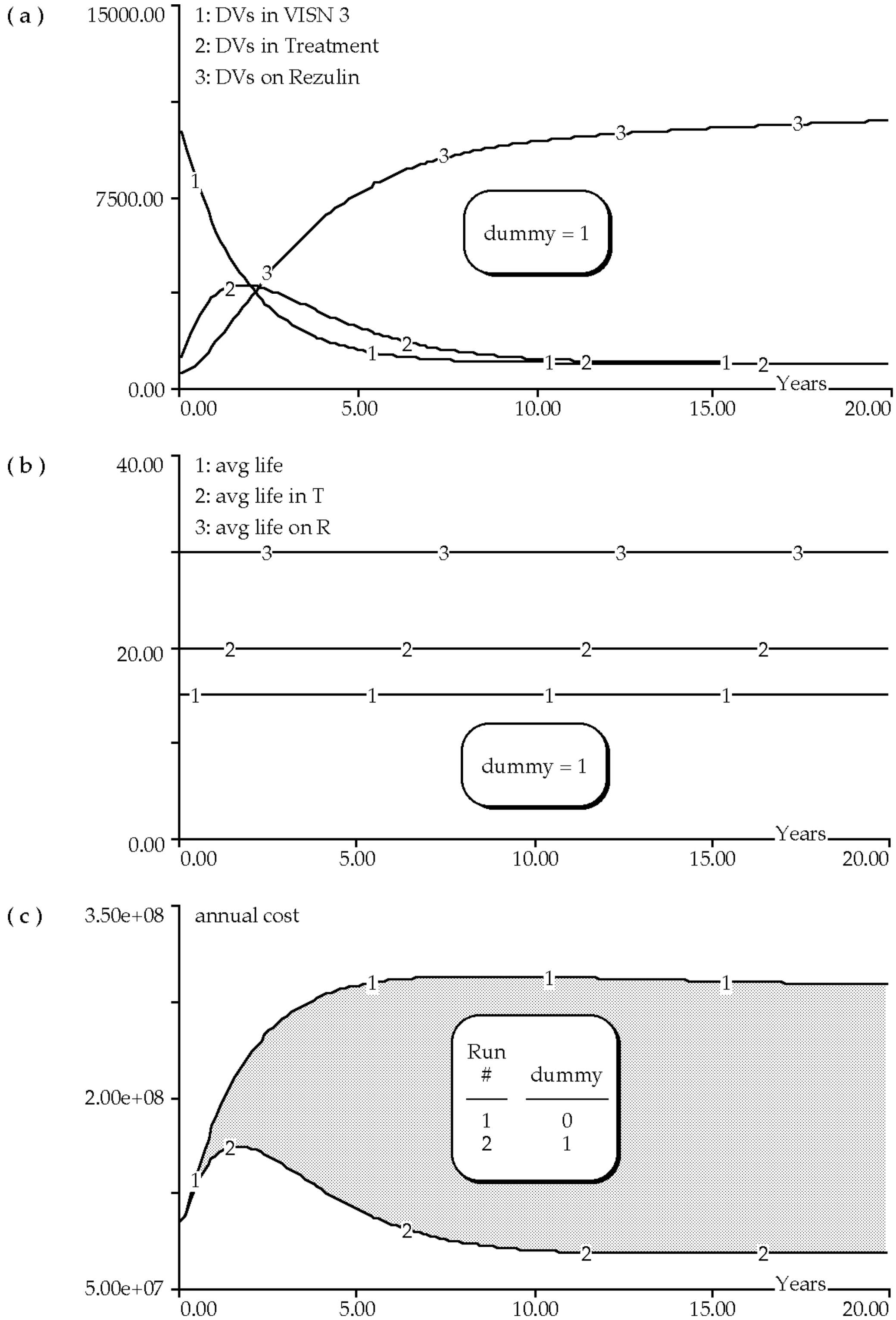
Fig. 3

Simulation output time-series graphs with current-state initialization and variable *dummy* = 0, 1



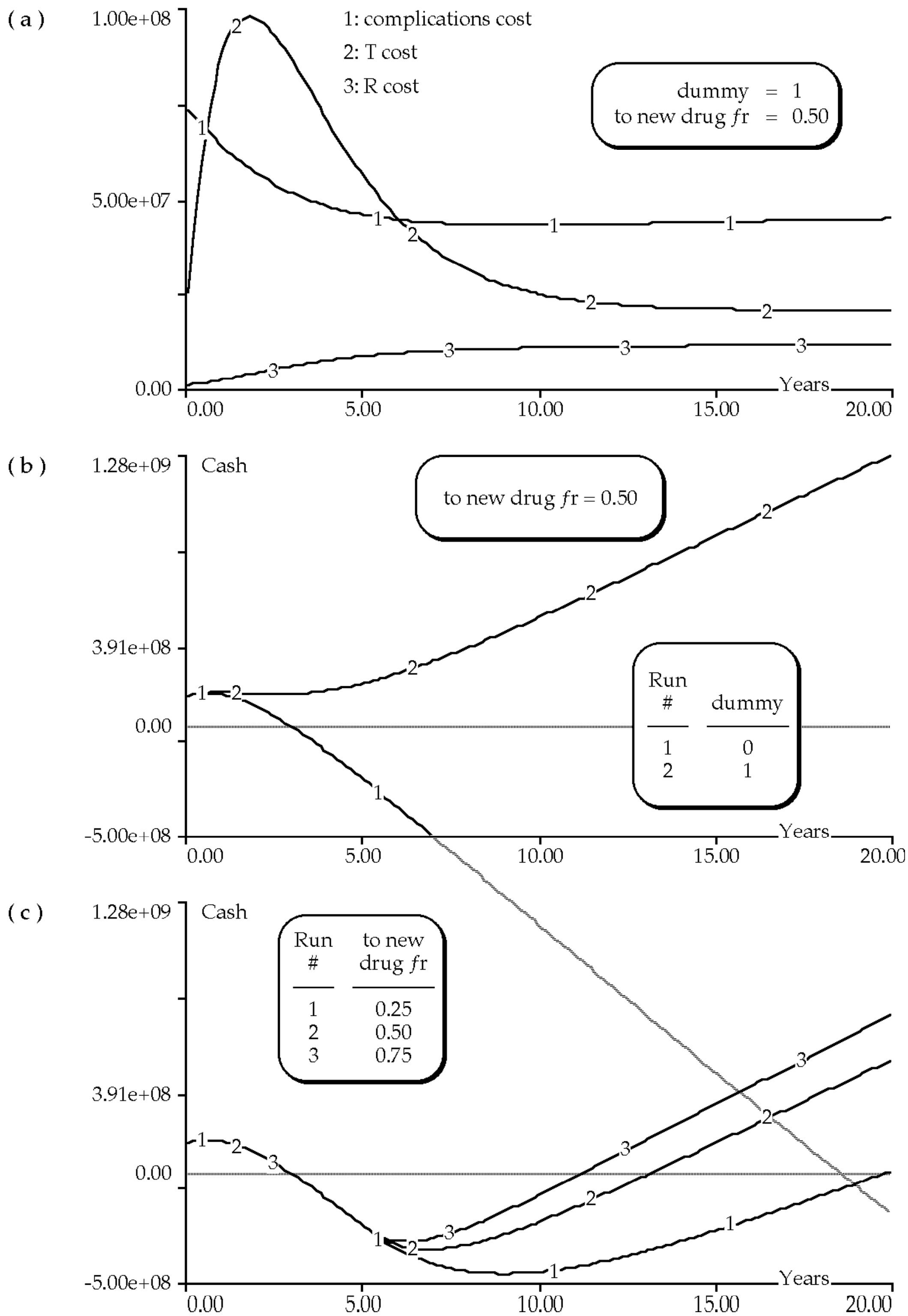
therapy, DVs in Treatment initially rise but decline quickly because some migrate to the new Rezulin drug (line #2, Fig. 4a). Their migration in turn

Fig. 4
Simulation output time-series graphs with current-state initialization and constant *to new drug fr* = 0.50



causes DVs on Rezulin to increase at a declining rate (line #3, Fig. 4a). Fig. 4b again shows the effectiveness of Rezulin therapy, attributed to the new

Fig. 5
Simulation output time-series *cost* and *Cash* graphs with current-state initialization



drug's ability to prolong the diabetic veterans' life by lowering their blood glucose and HbA1c level. Concerning Rezulin's efficiency, the shaded area of Fig. 4c shows the potential *annual cost* benefit VISN 3 can enjoy now that this new oral-antidiabetic drug therapy has become available. Without the new drug therapy, the *annual cost* rises and stays high (line #1, Fig. 4c), but with Rezulin, VISN 3's *annual cost* stays under control (line #2, Fig. 4c).

Looking at the *annual cost* components, one can see why using Rezulin yields a cost reduction. Figure 5a shows that while the *complications cost* declines as diabetic veterans seek treatment (line #1), *treatment cost* rises sharply at first precisely because more DVs move into treatment (line #2: *T cost*). Gradually, however, as more and more diabetic veterans start using Rezulin, *T cost* drops but it's still higher than the Rezulin cost (line #3: *R cost*, Fig. 5a). This does not happen simply because Rezulin-based therapy costs less but, more importantly, because it also prolongs diabetics' life and thereby reduces the *complications cost* of the disease.

The last two graphs of Fig. 5 look at VISN 3's *Cash* position through time. Specifically, line #1 on the comparative graph of Fig. 5b shows that *ceteris paribus*, without Rezulin (*dummy*=0), very soon VISN 3 may have no *Cash* left for diabetes treatment. The broken-line segment of the #1 *Cash* line follows a *dire-straights* trajectory very far below zero. Conversely, with the use of Rezulin (*dummy*=1), the veteran's network *Cash* position improves through time (line #2, Fig. 5b).

With the new oral-antidiabetic drug therapy enabled at time t=5 years, VISN 3 might still run into financial trouble due to Cash shortage. The veterans' network may still recover, however, thanks to Rezulin. How fast the recovery takes place will depend on the DV *migration fraction* (fr). The faster the network's diabetic veterans migrate from conventional insulin treatment to Rezulin therapy (by 25 to 50 to 75 percent), the faster VISN 3's *Cash* position moves from being negative to being positive again (Fig. 5c).

Conclusion

The system dynamics modeling process used here aimed at showing exactly how the new oral-antidiabetic drug Rezulin might prove itself to be an effective and efficient treatment for diabetes. The model built depicts relationships within VISN 3 among diabetic veteran sub-populations, depending on whether or not DVs seek treatment and are willing to switch from conventional insulin or other drug treatment to Rezulin therapy. The model also incorporates real-life statistical data, and assesses Rezulin's effectiveness and efficiency via performance variables such as *average life*, and *annual cost* and *Cash* position, respectively.

The simulation results show that indeed Rezulin is an effective drug. In all simulation experiments, diabetic veterans' average life is prolonged once they move from conventional insulin or other drug treatment to Rezulin therapy. Rezulin therapy is also an efficient anti-diabetic treatment, not only because it costs less than insulin and other anti-diabetic drugs but, more importantly, by prolonging life it also reduces the *complications cost* of diabetes. Rezulin use will help diabetics battle health care's rising cost.

Appendix: Model Equations

Level Variables

Cash(t) = Cash(t - dt) + (annual_revenue - annual_cost) * dt
INIT Cash = 151,457,218 {dollars}
DVs_in_VISN_3(t) = DVs_in_VISN_3(t - dt) + (new_DVs - to_treatment - death) * dt
INIT DVs_in_VISN_3 = 10000 {persons (**DV = diabetic veteran**)}
DVs_in_Treatment(t) = DVs_in_Treatment(t - dt) + (to_treatment - to_new_drug - death_in_treatment) * dt
INIT DVs_in_Treatment = 1000 {persons}
DVs_on_Rezulin(t) = DVs_on_Rezulin(t - dt) + (to_new_drug - death_on_Rezulin) * dt
INIT DVs_on_Rezulin = 500 * dummy {persons}

Rate Variables

annual_cost = complications_cost + T_cost + R_cost {dollars/year}
annual_revenue = funding_ƒr * annual_gov't_funds {dollars/year}
death = DVs_in_VISN_3 / life_expectancy {persons/year}
death_in_treatment = DVs_in_Treatment / (avg_life * T_gain {persons/year}
death_on_Rezulin = (dummy * DVs_on_Rezulin) / (avg_life_in_T * R_gain) {persons/year}
new_DVs = 500 {persons/year}
to_new_drug = to_new_drug_ƒr * DVs_in_Treatment * dummy {persons/year}
to_treatment = to_treatment_ƒr * DVs_in_VISN_3 {persons/year}

Auxiliary Variables

avg_life = DVs_in_VISN_3 / death {years}
avg_life_in_T = DVs_in_Treatment / death_in_treatment {years}
avg_life_on_R = DVs_on_Rezulin / death_on_Rezulin {years}
complications_cost = complications_cost_per_DV * (death + death_in_treatment + death_on_Rezulin) {dollars/year}
dummy = IF(TIME < 5) THEN(0) ELSE(1) {dimensionless, 0 or 1 variable}
R_cost = R_cost_per_DV * DVs_on_Rezulin {dollars}
T_cost = T_cost_per_DV * DVs_in_Treatment {dollars}

Constant Parameters

annual_gov't_funds = 1,009,714,793 {dollars/year}
complications_cost_per_DV = 100,000 {dollars/person}
funding_ƒr = 0.15 {dimensionless}
life_expectancy = RANDOM(12, 18, 123) {years (Set to 15 years for smooth graphs)}
R_cost_per_DV = 1,077 {dollars/year}
R_gain = 1.5 {dimensionless}
to_new_drug_ƒr = 0.5 {dimensionless}
to_treatment_ƒr = 0.5 {dimensionless}
T_cost_per_DV = 25,242 {dollars/year}
T_gain = 4/3 {dimensionless}