System Dynamics Model of A New Prenatal Screening Technology

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Abstract

The evaluated ELI-P Complex test is a biochemical system for pre-pregnancy/pre-natal screening used to determine the probability of pathology in pregnancy through the evaluation of the immunoregulatory state of fertile females. This work uses system dynamics (SD) as an assessment tool for the given technology and policy analysis. Simulation is designed to run at a relatively high level of aggregation for the time period between 2010 and 2035. It allows the dynamics of the model to be traced at the population (US) level of technology application in order to conduct an integrated policy analysis for prenatal care under various implementation scenarios of the ELI-P Complex. Simulation results clearly point to the benefits of the ELI-P Complex screening which helps monitor female reproductive health and achieve noticeable improvements in the overall health status of new generations. This work is result of collaboration with a well integrated network of clinicians, microbiologists and system modelers.

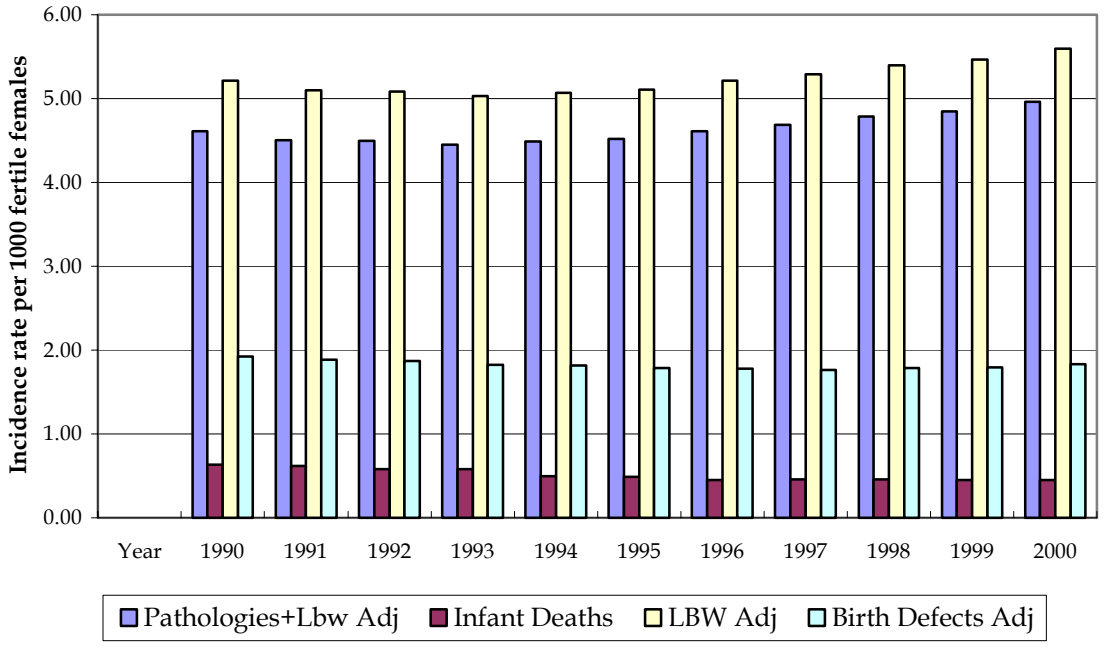
Introduction

Prenatal care in the US is not as efficient as in most developed countries and over the last ten years it has not demonstrated many satisfactory improvements. Increased spending on prenatal care and introduction of new technologies did not decrease the number of low birth weight newborns (LBW), pre-term births[1] or birth defects [1]. Every year about 120,000-150,000 U.S. babies are born with a birth defect (3-4% of newborns) [2,3] - the leading cause of infant mortality. 7.5% of children manifest a congenital defect by age 5 [4]. About 65-70% of birth defects have unexplained causes [3,5]. The social and economic impact of birth defects remains very troublesome and direct and indirect costs amount to billions of dollars annually [6]. Figure 1 summarizes pathological pregnancy outcomes over the 10 year period between 1990 and 2000.

[1] Infant mortality has been decreased through the use of advanced and expensive neonatal care units.

Data Source: OECD, March of Dimes

Figure 1
Pathological Outcomes of Pregnancy (US data)



Not considering genetic causes, which account for only 13% of all birth defects [7], it has been determined that a large number of birth defects occurs due to mothers' poor health [8,9,10,11]. Most of the time a woman and her physician may not be aware of some health problems that might exist unless a patient has a documented history of a chronic illness, detected infection, or another diagnosed condition before or at the beginning of pregnancy. However, a woman's body is not always at its best state to create a safe environment for the fetus and produce a healthy baby as a result.

Today, the science of birth defects prevention does not extend beyond anti-alcohol/anti-drug campaign, folic acid and healthy diet/exercise recommendation. Usually, only the risk group[2] undergoes genetic/hormonal counseling and very few population screening programs exist to lower the occurrence of birth defects. The rapid development of new technologies allows *detecting* (not preventing!)[3] of some birth defects (mostly of genetic nature), but the result is either an abortion (which is emotionally difficult for future parents) or a sick child. In rare cases, intrauterine treatment can improve the condition of a newborn, but for most conditions such treatment is not possible.

In addition, 13.4% of US females of fertile age live below poverty level, 11.9% do not receive adequate prenatal care (which increases risks since the basic care offered in the US at least manages to sustain the current figures of pregnancy outcomes), 22.7% of births are from women with less than 12 years of education, and around 14% of females of fertile age remain uninsured [12]. Waitzman *et al* in early 1990s estimated the economic costs of birth defects at ~US$8

[2] Women over 35 or those with history of genetic or hormonal problems.
[3] Non-invasive prenatal diagnostics technologies are under development: [www.safenoe.org]

billion per year [6]. Due to inflation, new procedures, and inclusion of other indirect costs, this figure is assumed to be significantly higher. US$36 billion each year is spent on special education programs for individuals with developmental disabilities [13]. In addition, the average cost of care for one person with mental retardation is US$1 million (in Y2003 dollars) and it is estimated that the lifetime costs for all people with mental retardation who were born in 2000 will total US$51.2 billion (in Y2003 dollars) [2]. The socio-economic burden produced by poor female health and poor pregnancy outcomes is obvious.

This research evaluates a screening technology developed by Russian bio-scientists at the Immunculus Medical Research Laboratories [15]. ELI-P Complex is a biochemical test system for pre-pregnancy/pre-natal diagnostics used to determine the probability of pathology in pregnancy. ELI-P Complex screening reveals immunoregulatory reproductive state of a woman. Abnormal test results indicate the presence of a chronic condition or an acute process, which may be harmful for the future fetus. Hence, screening fertile women planning pregnancy or in the first trimester with ELI-P Complex and treating those who have poor test results, can reduce the number of birth defects, increase the number of healthy newborns and decrease the number of newborns with pathologies [8,10,11,16]. Consequently, the application of this technology at the population level has a potential to revolutionize prenatal care, produce a noticeable economic impact, and improve the socio-demographic situation.

Data Source: Moscow Females 1992-1999 Poletaev, et al.

Figure 2
Pregnancy Outcomes of ELI-P Screened Females

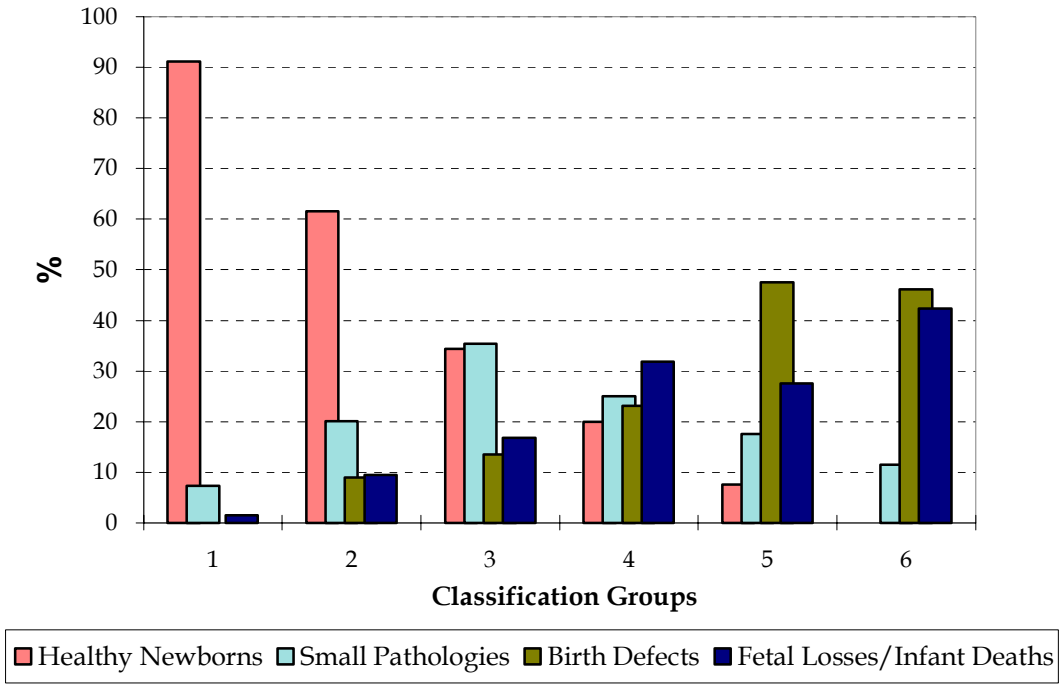


Figure 2 summarizes the results of clinical trials of the ELI-P Complex test conducted between 1992 and 1999. This seven-year study of pregnant women (N=2000) in the Moscow region has shown incredible benefits of the ELI-P test. Women who were screened with this technology

and placed in Group 1[4] (Figure 2) had over 90% of healthy newborns and women in Group 6 had no healthy newborns and over 80% (combined) outcomes of fetal deaths, stillbirths, miscarriages or newborns with birth defects. Other studies [18,19,20] on population groups in different regions confirmed these trends.

First and foremost, ELI-P Complex is an ***information technology***. It is not a treatment and it is not a device detecting a specific condition. It is a screening technology, providing physicians with the information about the patients' body state, specifically, the females' immunoregulatory status responsible for reproduction. Thus, ELI-P Complex should be integrated into an already developed screening/diagnosis/treatment framework since its aim is to augment the value of the already existing procedures. Currently women are undergoing a lot of unnecessary tests [1] or being treated with wrong medications during pregnancy [1,17], which can be harmful to the fetus or the mother, or the opposite: those women who should be given special attention are not examined and treated properly.

The aim of this research is to conduct a policy analysis (the process, through which alternative policies or programs that are intended to lessen or resolve social, economic, or physical problems are identified and evaluated [14]) for the introduction of the new (non-genetic) technology into pre-conception/prenatal care in the US using modeling and simulation. However, the actual implementation of the suggested policies in this study will requires a considerable amount of work, ranging from obtaining additional clinical trials data of the ELI-P Complex screening, to lobbying for funding and the promotion of this technology.

Modeling Process

The primary goal is to model one aspect of prenatal care (not the entire prenatal care system) where a new intervention (screening technology) can demonstrate its impact on pregnancy outcomes. The secondary goal is to create a simplified representation of reality, which can be understood not only by medical or system dynamics professionals, but by all stakeholders with the basic knowledge of concepts. The tertiary purpose is to design a set of policies for the future prenatal care in the US, which can help address some of the identified problems. Finally, the purpose of the model is to demonstrate an efficient method for early health technology assessment using system dynamics simulation.

System dynamics was chosen as a preferred modeling methodology for this project because it adopts a holistic approach and helps understand the basic structure of the system and the behavior it produces. Economic analysis can be more useful for healthcare technologies associated with treatments to demonstrate their financial performance. Preventive technologies

[4] ELI-P Complex Groups classification: The ELI-P Complex test detects the quantities of embryotropic auto-Abs to the eight reproductive antigens in the blood of females. It has been determined that women with good (normal levels of embryotropic auto-Abs) ELI-P Complex results (groups k1 and k2) have a much higher number of healthy children and very few newborns with small pathologies and even fewer if any with birth defects, while women in groups k5 and k6 have less healthy babies (most of whom develop various health problems in the future), high number of birth defects and many newborns with small pathologies. Women who are tested before pregnancy or during the first trimester and are placed in groups k3-k6, most of the time can be treated with widely-available medications to restore the activity of their embryotropic autoantibodies to a proper level, which significantly decreases the number of newborns with birth defects and increases the number of healthy newborns [8,11,19,20,21].

(diagnostics/screening tools) often cannot benefit from this analysis due to the lack of evidence; and this is when system dynamics modeling offers its superiority. Whilst evaluating ELI-P Complex, we must admit the lack of clinical trials data on different population groups. This makes statistical analysis and discrete event simulation inapplicable. However, we possess sufficient information to create an SD simulation for policymakers.

Table 1 summarizes the problem description, objectives and system boundaries of the Population Screening Model.

Table 1

Project Title	ELI-P Complex Early HTA Model
Problem Description	Up to 70% of birth defects remain unexplained. If birth defects are not of genetic nature, poor female health or behavior are considered to be the primary cause. Often a woman and her physician are not aware that a woman's body might not be at its best state to carry a future child. Birth defects and congenital abnormalities place a significant socio-economic burden on the society.
Objectives	Model long-term socio-economic benefits of the ELI-P Complex screening technology.
Period Considered	2005-2030
Reference Values	1985-2002
System Boundaries	US population, limited number of external factors. Excluded variables: decision to test, demand for treatment, female demographics, socio-economic status, age, lifestyle, ethical evaluation, suppliers, manufacturers, teratogen and natural factors, genetic screening, diseases/epidemic, insurance, public education programs, investment, legal considerations, prenatal care quality & effectiveness, screening accuracy

The time horizon chosen for the simulation is 25 years (2010-2035), which is sufficient to address the dissemination of technology, its adoption, and some of the effects.

At a high level of aggregation, the "client" of this model is the society; if we dissect the model, the client for some submodels may be either a female, or a given population group that undergoes the screening process. The source of the problem (birth defects and inborn pathologies[5]) is biological and evolutionary, and its outcomes produce a negative socio-economic impact. The list of causes contributing to the problem is extensive: genetics, teratogens, behavior, chronic or acute conditions, malnutrition before or during pregnancy, hygiene, ineffectiveness of prenatal care and low utilization rate, lack of awareness among women about healthy pregnancy and available procedures, screenings, tests, etc. The identification of how the problem (poor pregnancy outcomes) arises is out of scope of this research. The focus of this work is to take the bio-socio-economic situation as a starting point, recognize the existing problem and suggest how an intervention in the form of a new screening technology can address this problem.

We started the modeling process with the development of the qualitative models – causal loop diagrams. Figures 3 shows examples of the progression of our systems thinking exercise.

[5] Here birth defects are defined as severe structural defects; Inborn pathologies are the deviations of perfect health status where a child does not have a clearly expressed birth defect but may suffer from developmental problems, mental retardation, chronic inherited diseases, etc. (many of these pathologies are detected between 1st and 3rd years of life and not at birth.

Figure 3: Fragment of a Causal Loop Diagram 1

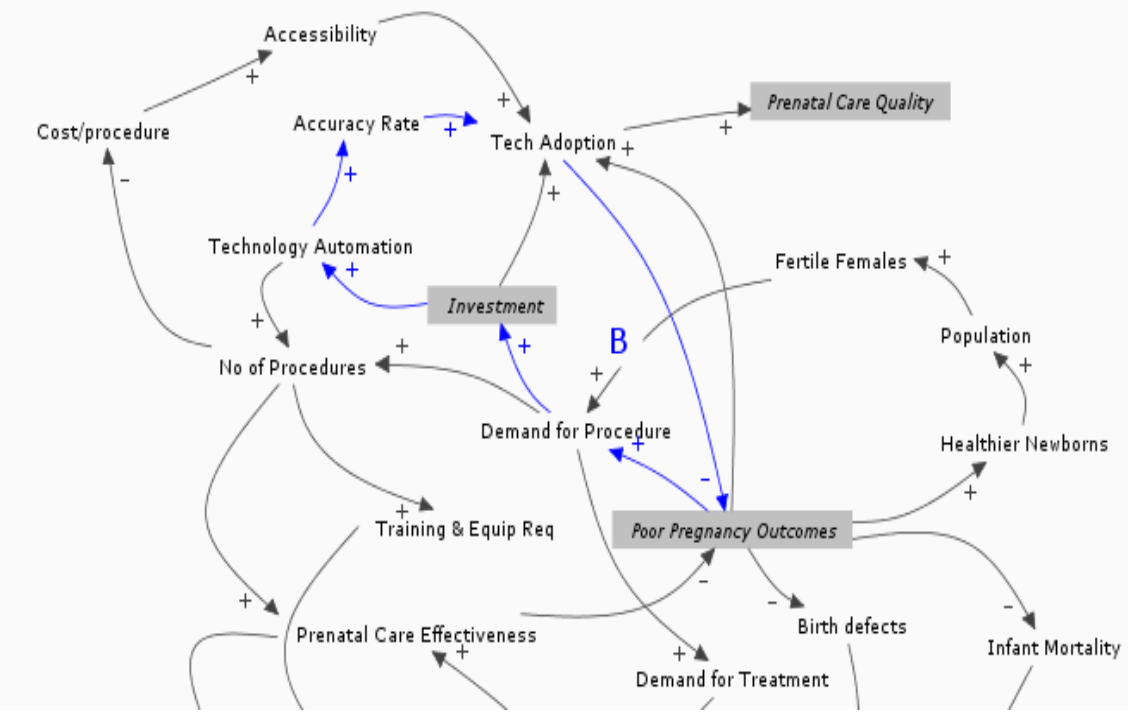
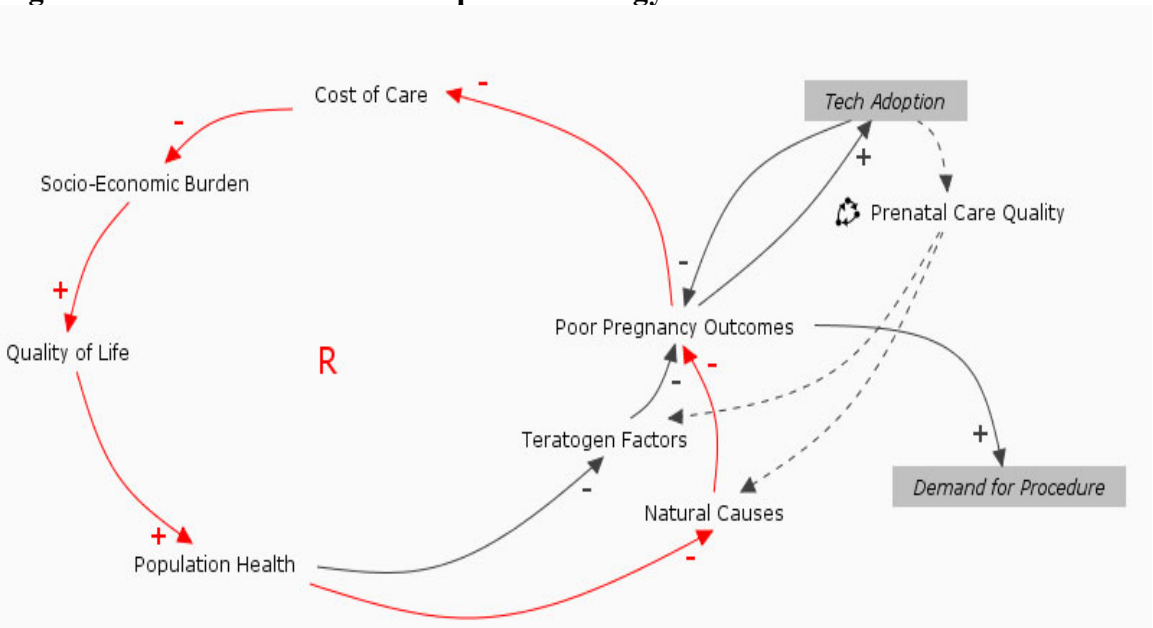


Figure 4: Basic reinforcement loop of technology innovation



Influence diagrams [causal loops] helped us identify gaps in knowledge and data, determine some parameters and yield interesting informative insights about the problem, thus providing the qualitative analysis for the development of the simulation.

Computer modeling is done using Consideo® and Stella® software. The quantitative part of the modeling begins with the parameter estimation, which was done using available data (derived

from literature review, clinical trials, economic and population indicators), experts' opinion, and informed guesses based on the accumulated knowledge. Then quantitative relationships among the variables are expressed in the form of equations and the information is entered into the computer simulation. In order to design a manageable model, the focus is only on the essential features and factors relevant to the questions at hand, thus the selection of variables is limited and where possible, variables are aggregated to give clarity to the model.

The Screening Technology Model has 96 system parameters, of which 19 are state variables and 7 are graphical functions. Figures 5 (part of the model) summarizes the model structure in terms of stocks and flows. The ELI-P Complex Population Screening simulation consists of two submodels: 1) pregnancy onset and screening and 2) pregnancy outcomes.

Each equation and each parameter in the model (Table 2) is described with a convincing amount of evidence supporting the nature of relationships among parameters and the actual choice of variables. The evidence is drawn from expansive literature reviews, experts' opinions, historical data, and currently available statistical data. The Population Screening model has 62 equations.

The Aggregate Model tracking improvement of female health, is designed for 40 years (2010-2050) to demonstrate population health re-generation results. This model traces pregnancy outcomes as a feedback to the overall female health and it is an aggregate version of the Population Screening model presented above. It has been developed as an auxiliary tool to demonstrate the potential of the ELI-P Complex technology. The change of scale from 25 years to 40 (2010-2050) allows tracing the feedback effects on female health improvement. In the simplified Aggregate model the ELI-P Complex screening is presented as a binary variable to evaluate pregnancy outcomes without any changes (current system) and with the technology intervention. Figure 6 depicts the stock and flow structure of this model.

Table 2 Estimates of Selected Parameters

Healthy Women [61,660] in thousands	H	The initial value for the stock was forecasted in Excel for the year 2010 from OECD Health DATA 2004 (77% of all women in the age cohort 15-49)
Unhealthy Women [18,418] in thousands	U	The initial value for the stock was forecasted in Excel for the year 2010 from OECD Health DATA 2004 (23% of all women in the age cohort 15-49)
Fertile Women [80,078] in thousands	N	The initial value for the stock is forecasted in Excel for the year 2010 from OECD Health DATA 2004
Planning Pregnancy [3,467] in thousands	PP	The initial value for the stock is estimated number of planned pregnancies for 2010 considering that 53% of all pregnancies that year will be planned.
Not Planning [77,571] in thousands	MPL	Fertile women not planning pregnancy.
Pregnancy Rate Not Planning Entering PC [0.027]	rNP	Overall pregnancy rate was calculated from taking the population data (females age 15-49) OECD Health DATA 2004 and pregnancy statistics from National Vital Statistics Report, Vol. 52, No. 23, June 15, 2004. Average pregnancy rate was derived (~0.084); 85%-53%=32% (prenatal care utilization-planning rate) 32% of 0.084 is the rate at which not planning women get pregnant in the age cohort 15-49.

Planning Rate [0.044]	rPL	According to http://www.plannedparenthood.org/ only 51% of pregnancies were planned in 2000. The rate in simulation is adjusted to 2010. 53% of all planned pregnancies for year 2010 = 0.044 of fertile females in the age cohort 15-49
Not Enrolling in PC Fraction [0.04- rNP]	nPC	0.04 fraction = 100% of pregnant non-planning pregnancy women
Poor Test Results [0.2]	PtrPL PtrNP	According to the clinical trials of the ELI-P Complex, ~20% of females have ELI-P indicators out of the normal range.
Growth Rate (fertile females) [0.0085]	gr	Population growth rate is calculated from the Census forecast available at [http://www.census.gov/ipc/www/ usinterimproj/natprojtab01a.pdf] and adjusted to the growth rate for the pool of females in the age cohort 15-49 for the years 2010-2035
Pregnancy Loss Rates	PLrS PLrU	National Vital Statistics Report, Vol. 52, No. 23, June 15, 2004. 2000 data indicates 21% of aborted pregnancies. The adjusted number for 2010 assumes a decrease in induced abortions. 2000 data indicates 16% in fetal losses. Pregnancy Loss rates are combined rates of abortions and fetal losses adjusted to 2010 [0.31]. Graphs 5&6 in Table 4.10 represent the changes in pregnancy losses over time as screening is being implemented.
Multiple Births Fraction [0.035]	mb	[http://www.cdc.gov/nchs/fastats/multiple.htm] 2002 Data
Immigration Rate [0.002]	imr	According to Migration News[http://migration.ucdavis.edu/ mn/comments.php?id=1246_0_2_0] net immigration in the US between 1990-1996 was ~690,000 per year, which is about 246 per 100,000 of US population.
US Population [308,936] in thousands	P	Population forecast for 2010 was taken from US Census data: [http://www.census.gov/ipc/www/usinterimproj/natprojtab01a.pdf]
Cost per BD Case [66,000] $US	cD	According to California birth defects registry, cost of Birth Defects was estimated ~ US$8billion per year [1992]. The average cost per BD was calculated from 3% (of total births) birth defects occurring every year.
Cost per Pathology Case [15,000] $US	cP	The average cost per Pathological birth outcome was assumed to be US$15,000. 7.5% (of total births) pathological pregnancy outcomes occur every year (March of Dimes).
Cost of Treatment [200] $US	ct	Average price of treatments which are listed in Table 4.6
Cost per Test [22] $US	ce	Estimated in [21]
Death Rate Healthy Women[0.0005] Death Rate Unhealthy Women [0.0022]	drH drU	Deaths data is taken from National Vital Statistics Reports, Vol. 53, No. 15, February 28, 2005. In the age cohort 15 - 49 death rate is ~272 per 100,000 females (0.00272).
Infant Mortality Rate [0.0058]	ir	OECD Health Data 2004; 2001 - 6.8 deaths per 1000 life births. Rate adjusted for 2010-2035
Death Rate [0.0084]	dr	Deaths data is taken from National Vital Statistics Reports, Vol. 53, No. 15, February 28, 2005 DR for 2003~840 per 100,000 of US population

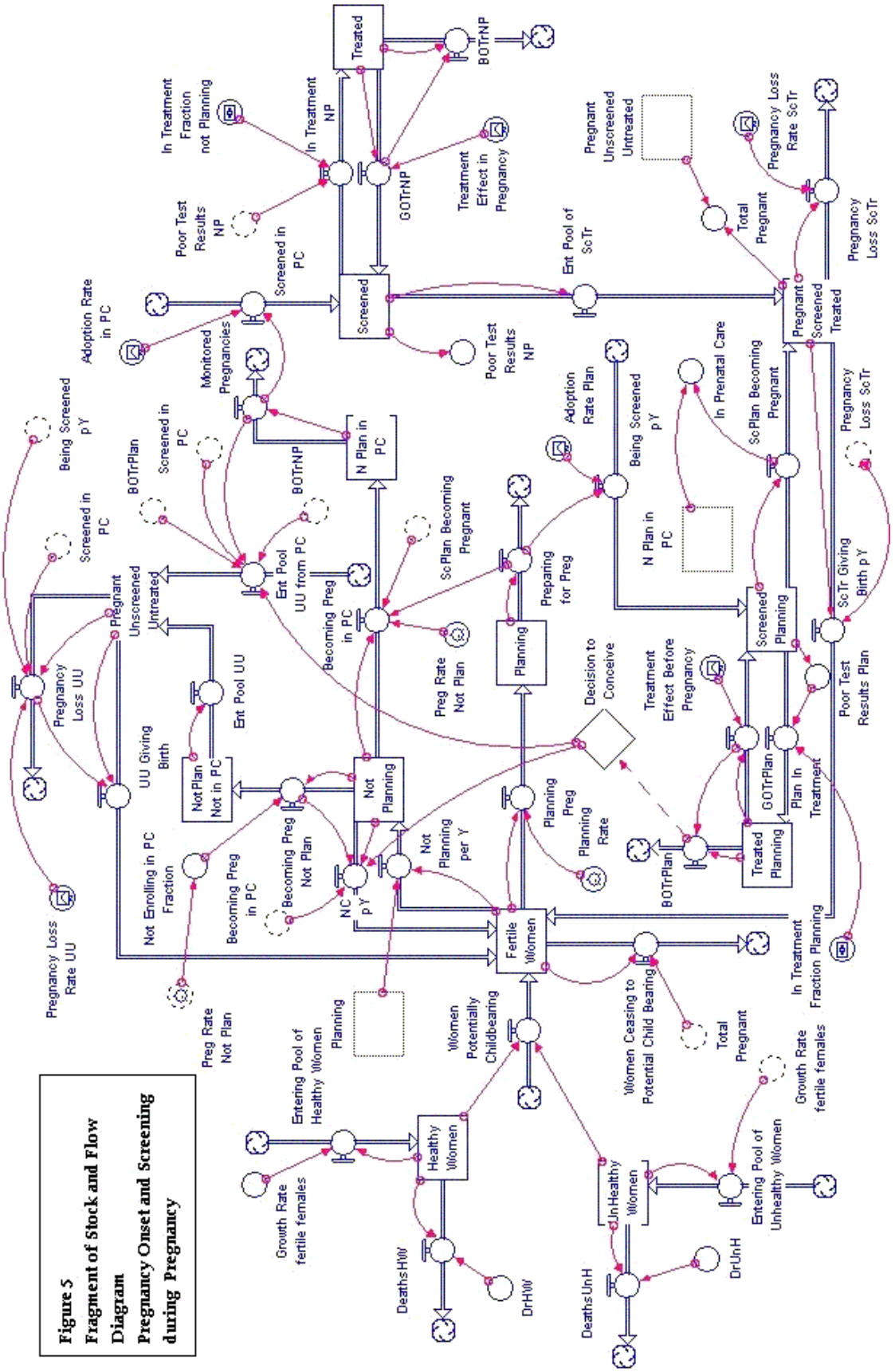
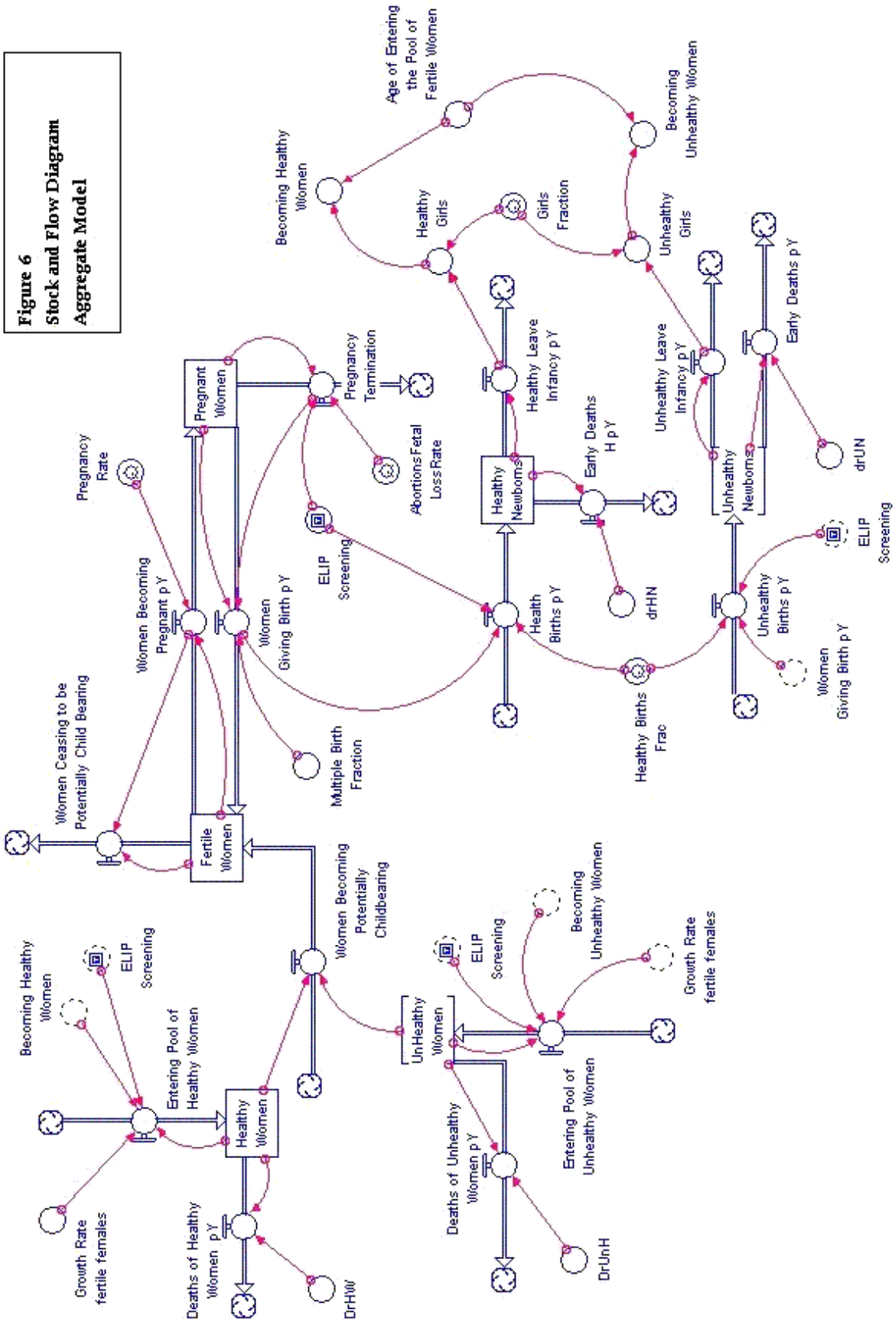


Figure 5
Fragment of Stock and Flow Diagram
Pregnancy Onset and Screening during Pregnancy

Figure 6
Stock and Flow Diagram
Aggregate Model



Results

Figures 7 and 8 present selected graphical outputs of the simulation. For the base case scenario the S-shaped technology adoption curve is chosen, where the full integration of the ELI-P Complex screening into clinical practice occurs around the year 2030. The base case run shows that the number of healthy newborns increases from 3,898,000 to 5,511,000 in the 25-year period while the number of newborns with pathologies and birth defects decreases from 349,000 to 282,000 and from 141,000 to 139,000 respectively. While the decrease in the actual number of newborns with pathologies and birth defects does not seem to be as great as expected, we have to keep in mind that in 25 years the total number of newborns increases by ~1,617,000, relative to which, the decrease in birth defects and births with pathologies by the year 2035, demonstrates significant improvement in pregnancy outcomes, compared to the year 2010.

Figure 7 Graphical Output Base Case: Pregnancy Outcomes

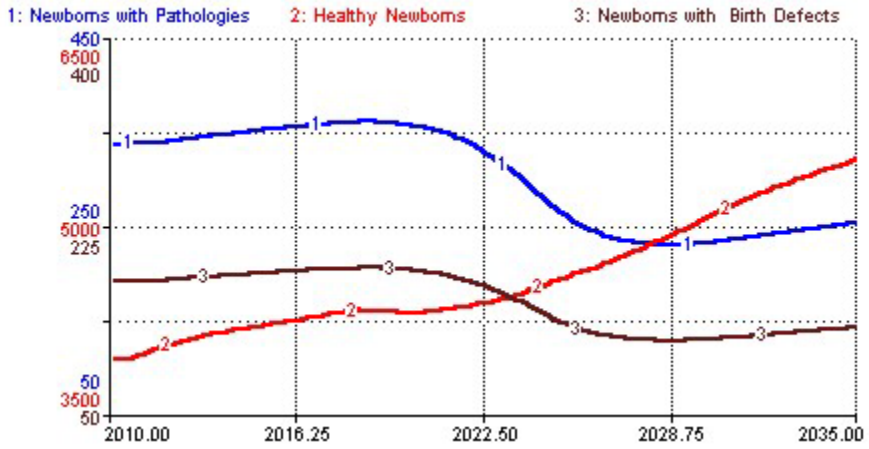
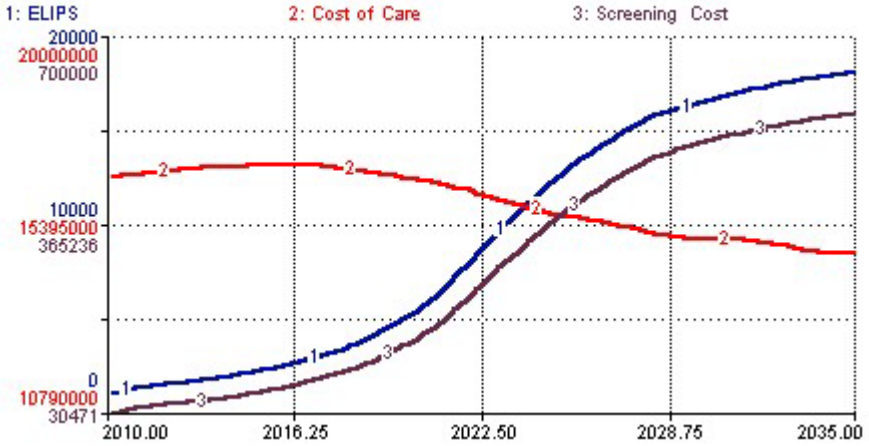


Figure 8 Graphical Output Base Case: Costs



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pathologies by the year 2035, demonstrates significant improvement in pregnancy outcomes, compared to the year 2010. During this period the simulation shows that the US population is expected to increase from 308,936,000 to 381,677,000, which is consistent with the US Census forecast[6]. By the year 2035 there will be ~18.2 million ELI-P Complex procedures performed per year and the cost of screening will be ~ US$564 million (in Y2005 dollars). In this study inflation is not taken into consideration and costs are not discounted. This is a game simulator, and the user is free to choose the cost per test and the cost per treatment and set adjusted values, if she has more accurate estimates at her disposal. According to the base run, the cost of care under the given settings can be brought down from US$14.5 to US$13.4 billion (in 2005 dollars) between the years 2010 and 2035.

Model Validation

The validation of the model is performed through a number of tests: direct structure test, extreme-condition test, parameter verification test, and experts' opinion. The behavioral validation is performed by assessing the quality of historical fit: after changing the initial settings in the simulation to 1985 data, the model is run to produce the outputs up to the year 2000. The results of this simulation are compared to the actual historical data. Finally, sensitivity analysis is performed to assess uncertainty of the estimated parameters and relationships between the structure and the behavior of the model.

After the analysis of the model's structure is performed using a structure-confirmation test and a parameter-confirmation test, the model's behavioral validity is then assessed by running the simulation on reference data (1985-2000) (the results are depicted in Table 3), testing it for various extreme conditions and conducing sensitivity analysis to identify parameters which have significant impacts on the model's behavior. As a part of the validation process, the model is checked for consistency and examined by experts from fields of system dynamics and preventive medicine. The Aggregate model is evaluated in a similar manner.

Table 3 Numerical Comparison of Simulation Output and Historical Data

YEAR	Fertile Women		Pregnant		Newborns		Population	
	Sim	*Actual*	*Sim*	*Actual*	*Sim*	*Actual*	*Sim*	*Actual*
1985	63,742	63,742	6,144	6,144	3,761	3,761	237,924	237,924
1989	64,872	66,536	6,395	6,527	3,838	4,041	248,228	246,819
1993	66,843	69,381	6,518	6,494	3,947	4,000	258,699	259,919
2000	70,778	73,744	6,397	6,401	3,937	3,935	278,372	282,224

Within the context of this research and the developed dynamic hypothesis the model did not fail any of the validation tests hence, it can be concluded that the model is valid.

Policy Analysis

Using "what if" analysis, the models' behavior is evaluated for new insights, which yield suggestions for policy generation. The integrated approach to policy analysis allowing

[6] US Census Population Forecast [http://www.census.gov/ipc/www/usinterimproj/natprojtab01a.pdf]

continuous monitoring and evaluation of policies over time, is suggested to further carry out the introduction of the ELI-P Complex into the national prenatal care system.

The graphic interface developed for both models allows for quick and easy creation of various "what if" scenarios. Below is an example of one scenario used to evaluate our model.

***What if* the adoption rate of this technology does not follow the S-shaped growth but remains around 20%?**

Under these settings the simulation produces expected results: the number of healthy newborns decreases, while the number of unhealthy newborns increases. The total number of newborns decreases slightly as well since the benefits of treatment recede and the number of fetal losses increases. Figures 9 and 10 summarize the outputs of the simulation for scenario 1. In both, Run 1 is the original run under the S-shaped growth (adoption rate up to 85%) and Run2 is an output under the adoption level depicted in Figure 6.1a.

Figure 9 Healthy Newborns Scenario 1

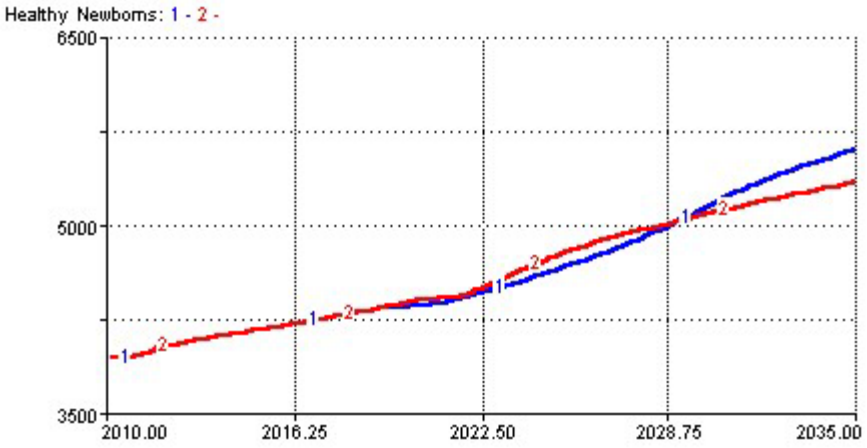
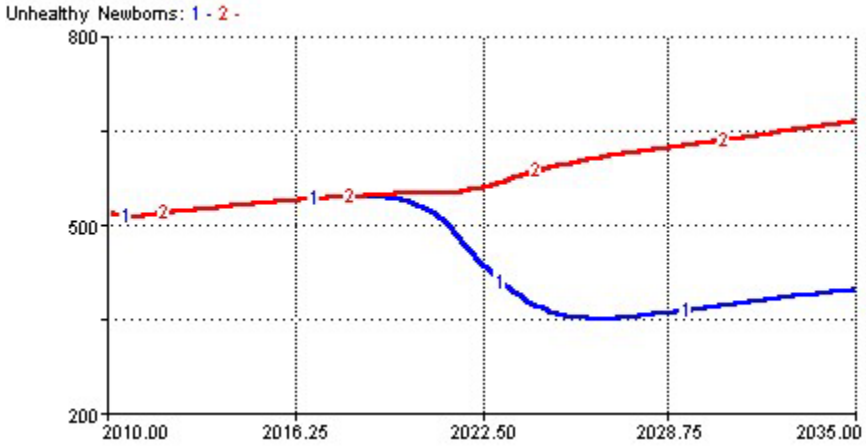


Figure 10 Unhealthy Newborns Scenario 1



The simulation responded correctly to all the changes in five developed scenarios. Further policy analysis helped us produce the following recommendations:

Policy Suggestion 1 Large clinical trials should be carried out to determine technology's performance, accuracy and benefits in order to identify the proper course for its adoption. The simulation suggests that population level of adoption (~85% of pregnant women and ~65% of planning pregnancy women) would be the most efficient and effective.
Policy Suggestion 2 If the technology is in the implementation phase at the population level, there should be all the incentives created to encourage women to screen *before* getting pregnant and get treated if necessary.
Policy Suggestion 3 The network of independent service providers is more innovative and efficient in a long run. The hierarchy of existing health care system is faster and better for control of established standards. Thus, the first one may be recommended for the industrialized countries, and the second one for the developing world.
Policy Suggestion 4 More research should be conducted to identify proper treatments restoring female immunoregulatory systems and producing beneficial results on pregnancy development.

The evaluation of the simulation results for the Year 2035 allowed us to calculate the cost per case prevented. When the Screening Cost reaches US$564,552,000, the Number of Procedures equals to 18,166,000, and the number of Birth Defect Cases Prevented is 53,000, while Other Costs constitute 1/5 of the working capital and are equal to US$69,999,120.

$$Cost\ /\ preventedCase = \frac{InterventionCost}{Cases\ \mathrm{Pr}evented} = \frac{564{,}552{,}000 + 69{,}999{,}120}{53{,}000} = 11{,}972$$

In order for technology to be considered cost-effective, it has to cost under $60,000 per case avoided, thus the intervention of the evaluated screening is highly cost-effective.

The proposed methodology is well suited to examine the dynamic effects of policy initiatives in prenatal care. It helps answer the questions of how the innovative technology can be implemented in the US for the population-wide screening and how such intervention can affect the socio-economic situation.

Conclusions

US prenatal care at the beginning of the 21st century is costly and rather cultural than effective: the consequences of unsuccessful pregnancies, birth defects and children with congenital defects that become apparent later in life, have very high economic and social costs [1]. Initial investment into the introduction and dissemination of the ELI-P Complex technology and screening costs per year are estimated to be significantly lower than the savings that result from the number of birth defects and pathological pregnancy outcomes prevented.

This work provided an enriched model of technology assessment, in order to equip policymakers with a proper tool to influence its' the future and propose various paths for adoption. Simulations developed in this research can be used as a framework for producing sophisticated policy analysis tools for prenatal care decision-making.

The creation of models and simulations in such fields as healthcare is impossible without close collaboration of stakeholders. The major benefit during the process of this simulation development came from successful networking among model-builders and experts in the field. Using system thinking environment helped us find many new ideas, learn to think about trivial problems in new domains and use the participants' abilities to produce a decision-making system.

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