THEORETICAL MODELS OF AGING

SANTA FE INSTITUTE

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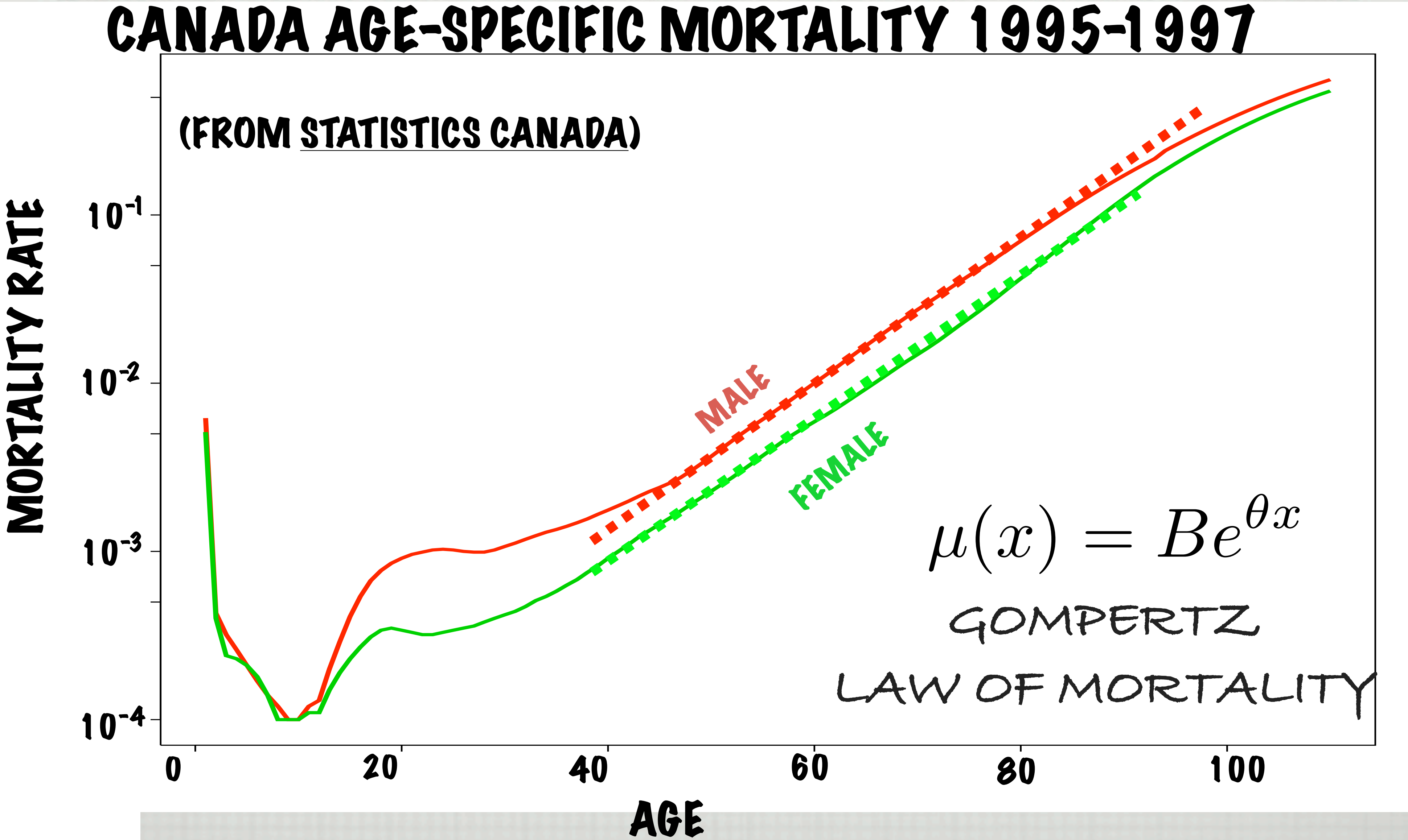
PETER MEDAWAR BUILDING

WHAT IS A MODEL OF AGING?



ANOTHER CLASSIC: STREHLER-MILDVAN MODEL

- DECLINE OF "VITALITY" LINEAR WITH AGE
- ORGANISM EXPERIENCES RANDOM, NORMALLY DISTRIBUTED "CHALLENGES"
- DEATH COMES WHEN A RANDOM CHALLENGE EXCEEDS VITALITY. IMPLIES GOMPERTZ MORTALITY
- UNSATISFYING, ESPECIALLY BECAUSE THE CRUCIAL AGING COMPONENT IS NOT AUTONOMOUS, BUT IS PUT IN AS A CLOCK-DRIVEN ASSUMPTION.

LEVELS OF MODELS

- MOLECULES/GENES
- INTERACTION MODULES
- ORGANELLES
- CELLS
- TISSUES

- ORGANS
- ORGANISMS
- POPULATIONS
- ECOSYSTEMS

EVOLUTION

MULTIPLE TIMESCALES TOO

MODELLING QUESTIONS

- CAN WE SEPARATE TIME-SCALES?
- CAN WE SEPARATE LEVELS OF ORGANIZATION?
- CAN WE TREAT DIFFERENT LEVELS WITH A UNIFIED APPROACH?
- WHAT ARE THE ESSENTIAL TRADEOFFS?
- WHAT LINK (IF ANY) IS THERE BETWEEN FUNDAMENTAL EVOLUTIONARY TRADEOFFS, THE TRADEOFFS WE SEE IN LABORATORY MUTATIONS, AND FACULTATIVE TRADEOFFS?

KINDS OF MODELS

- CONCEPTUAL
- SIMPLE SIMULATED
- SIMPLE THEORETICAL
- COMPLEX SIMULATED (SOME FEATURES MAY BE ANALYZED THEORETICALLY)
- DATA-DRIVEN

GOALS OF MODELS

- FUNCTIONAL
- DEFINITIONAL/PREDICTIVE
- TELEOLOGICAL - OPTIMIZATION
- TELEOLOGICAL - ENTROPIC

FUNDAMENTAL OBJECT OF AGING

- ☐ DAMAGED PROTEINS
- ☐ SOME OTHER JUNK COMPONENTS
- ☐ FREE RADICALS/ ANTIOXIDANTS
- ☐ SOMATIC MUTATIONS
- ☐ DAMAGED MITOCHONDRIA
- ☐ CANCER VS. GROWTH BALANCE
- ☐ LOSS OF HOMEOSTASIS
- ☐ DEPLETION OF STEM CELLS
- ☐ MUTATION ACCUMULATION
- ☐ LOSS OF STRUCTURAL INTEGRITY/ SYNCHRONIZATION
- ☐ ENERGY BUDGET
- ☐ SOMETHING ELSE

SOME FACTS

- SENESCENCE IS COMMON, BUT PERHAPS NOT UNIVERSAL
- SENESCENCE DOES OCCUR IN THE WILD
- MANY ORGANISMS HAVE SIMPLE MUTATIONS AVAILABLE WHICH SUBSTANTIALLY EXTEND LIFE. DO THEY SLOW <u>AGING</u>?
- MANY (BUT NOT ALL) ORGANISMS SHOW EXTENDED LIFESPAN AND RETARDED AGING UNDER CALORIC RESTRICTION
- THE GOMPERTZ PATTERN FITS HUMAN MORTALITY RATES EXTREMELY WELL -- OTHER ORGANISMS TO SOME EXTENT
- MORTALITY RATES ARE TYPICALLY HIGH EARLY IN DEVELOPMENT

GENERAL PRINCIPLES

- EVOLUTIONARY: DELETERIOUS EFFECTS AT LATER AGES ARE LESS STRONGLY SELECTED AGAINST
- ANTAGONISTIC PLEIOTROPY AND MUTATION ACCUMULATION
- THEREFORE, SOME KIND OF EARLY/LATE TRADE-OFF: ENERGY, REPAIR/INTEGRITY, GROWTH/ORDER
- AGING REPRESENTS A FAILURE OF HOMEOSTASIS
- AGING REFLECTS THE ACCUMULATION OF SOME KIND OF DAMAGE
- REPAIR IS IMPERFECT, COSTLY, AND SHOWS DIMINISHING RETURNS

MATHEMATICAL METHODS

- GRAPH THEORY/NETWORK THEORY
- DYNAMICAL SYSTEMS (SMALL VS. LARGE DIMENSION) - MORTALITY REPRESENTED AS SYSTEM CATASTROPHE
- MARKOV PROCESSES (CLASSICAL, TREE-INDEXED, AND MEASURE-VALUED)
- DYNAMIC PROGRAMMING
- MATRIX METHODS / RANDOM MATRICES

STATISTICAL METHODS

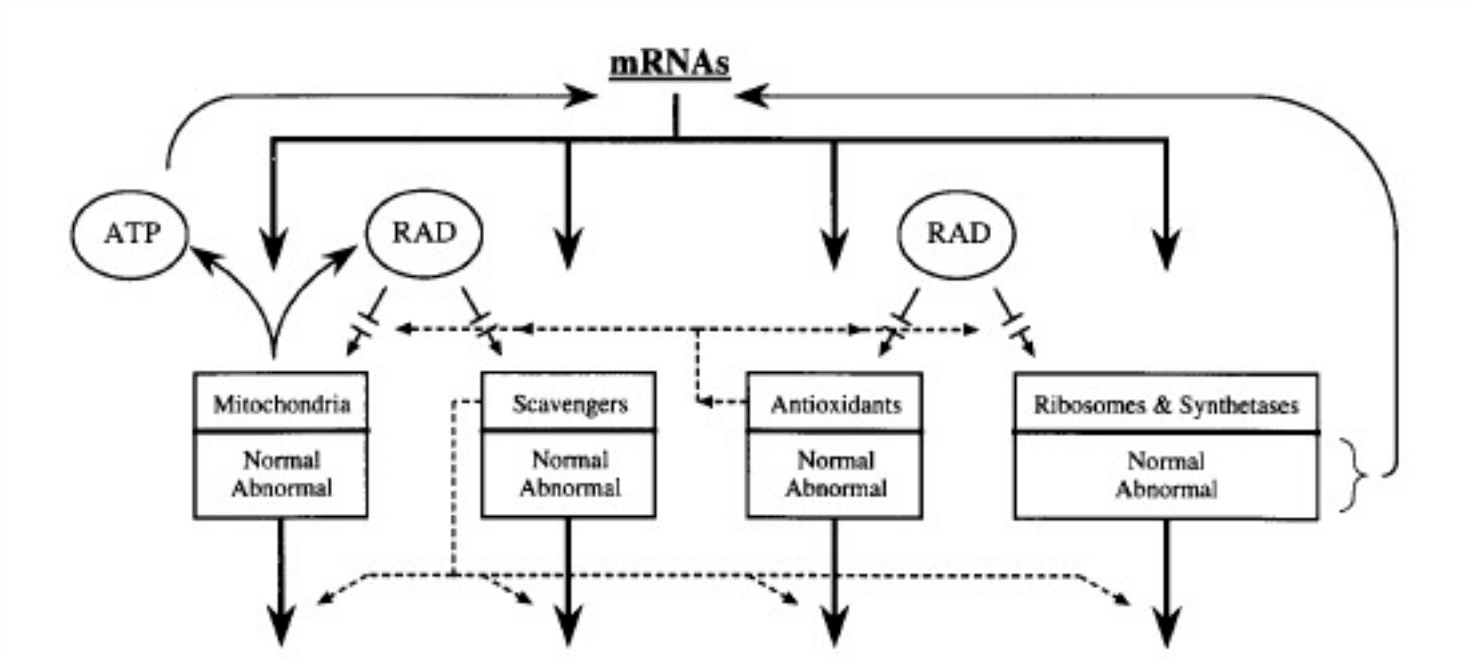
- ☐ SURVIVAL ANALYSIS
- ☐ MAXIMUM LIKELIHOOD
- ☐ BOOTSTRAPPING
- ☐ TIME-SERIES

WHAT IS THE QUESTION TO WHICH THE THEORY OF AGING WOULD BE AN ANSWER?

- IT IS INDEED REMARKABLE THAT AFTER A SEEMINGLY MIRACULOUS FEAT OF MORPHOGENESIS A COMPLEX METAZOAN SHOULD BE UNABLE TO PERFORM THE MUCH SIMPLER TASK OF MERELY MAINTAINING WHAT IS ALREADY FORMED. -- G. WILLIAMS (1957)
- THE DECLINE IN OLD-AGE MORTALITY IS PERPLEXING. WHAT BIOLOGICAL CHARTER PERMITS US (OR ANY OTHER SPECIES) TO LIVE LONG POSTREPRODUCTIVE LIVES?
  --J. VAUPEL ET AL. (1998)

MARS MODEL

- MITOCHONDRIA, ANTIOXIDANTS, REACTIVE SPECIES (KIRKWOOD/KOWALD 1996)
- MEDIUM-DIMENSIONAL DYNAMICAL SYSTEM
- MOLECULE TO CELL LEVEL
- SALVAGED CLASSIC "ERROR PROPAGATION" MODEL: ERROR RATE INCREASES WITH DETERIORATION OF MITOCHONDRIA, CROSSES THRESHOLD



CARDIAC AGING MODEL

- EXAMPLE OF INTERMEDIATE LEVEL OF MODELLING

- STEFANOVSKA (2009): BASED ON LONG, CAREFUL STUDY OF CARDIOVASCULAR SYSTEM AS LOW-DIMENSIONAL NONLINEAR DYNAMICAL SYSTEM OF COUPLED OSCILLATORS

- FINDS SIGNAL OF AGING IN MUTUAL MODULATION OF RESPIRATORY AND CARDIAC FREQUENCIES

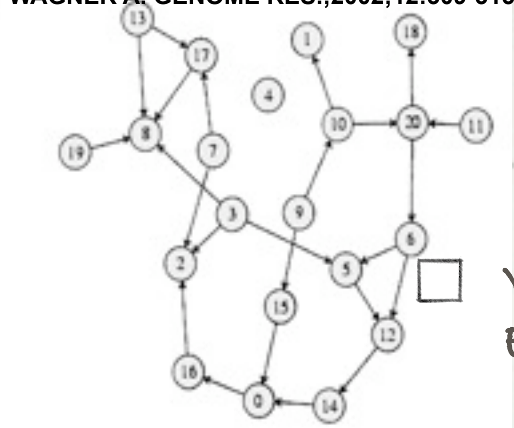
- THERE ARE MANY SUCH MODELS -- MOSTLY PRACTICAL, MEDICAL DRIVEN. E.G., WEINBERG ET AL (2009) MODEL OF AORTIC VALVE AGING

NETWORK MODELS

SIMPLIFIED DYNAMICAL SYSTEMS

- DYNAMICS ARE ALL IN THE NETWORK TOPOLOGY
- NO TIMING OR STRENGTH OF INTERACTIONS
- MAY BE A USEFUL SIMPLIFICATION

MICRO-INTRODUCTION TO NETWORKS


WAGNER A. GENOME RES.;2002;12:309-315

- VERTICES ARE THE OBJECTS (GENES, PROTEINS, ETC.)
- EDGES ARE INTERACTIONS (MAY BE DIRECTED)
- DEGREE OF A VERTEX IS THE NUMBER OF VERTICES IT'S CONNECTED TO (CF. IN-DEGREE, OUT-DEGREE)
- COMPONENT=CONNECTED GROUP OF VERTICES
- RANDOM GRAPH EXAMPLES: ERDOS-RENYI (CONNECT VERTICES INDEPENTLY), PREFERENTIAL-ATTACHMENT
- PREFERENTIAL-ATTACHMENT MAKES POWER-LAW NETWORK (ALSO CALLED SCALE-FREE NETWORK)

HUGE EXPERIMENTAL SHIFT: HIGH-THROUGHPUT TECHNOLOGIES

- NEED TO MINE GENE-EXPRESSION, PROTEIN-INTERACTION, SEQUENCE DATA TO GENERATE THE "MASTER NETWORK"
- SOME DATA PUBLICLY AVAILABLE (CAVEAT: SEE BELOW)
- DATA ARE VERY NOISY: HARD TO GET REPLICABLE RESULTS
- ALLOWS NEW QUESTIONS, NEW KINDS OF MODELS, BUT MAY BE EVEN HARDER TO ANSWER FUNDAMENTAL QUESTIONS BENEATH SO MUCH DETAIL
- "CHINESE NP NETWORKS"

PROMISLOW: PLEIOTROPY AND PROTEIN NETWORK

- HYPOTHESIS: ANTAGONISTIC PLEIOTROPY PREDICTS "MORE HIGHLY CONNECTED PROTEINS WILL BE MOST LIKELY TO EVOLVE AN ASSOCIATION WITH SENESCENCE."
- CAREFUL STATISTICAL TESTING: GENES ASSOCIATED WITH "AGING-RELATED" MUTATIONS DO HAVE HIGHER DEGREES THAN GENES ASSOCIATED WITH OTHER MUTATION SCREENS
- PROBLEMS: WHAT IS AN AGING-RELATED MUTATION? ARE THE MUTATIONS THAT SHOW UP IN SCREENS LIKE THE MUTATIONS THAT DRIVE EVOLUTION?

BIBLIOGRAPHIC PROBLEM: AGE MUTATION INFORMATION REFERRED TO AGEID DATABASE

Science AAAS | Magazine | News | Signaling | Careers | Multimedia | Collections

SAGE KE *Science of Aging Knowledge Environment*

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Home > SAGE KE Home > Highlights > Genes/Interventions Database

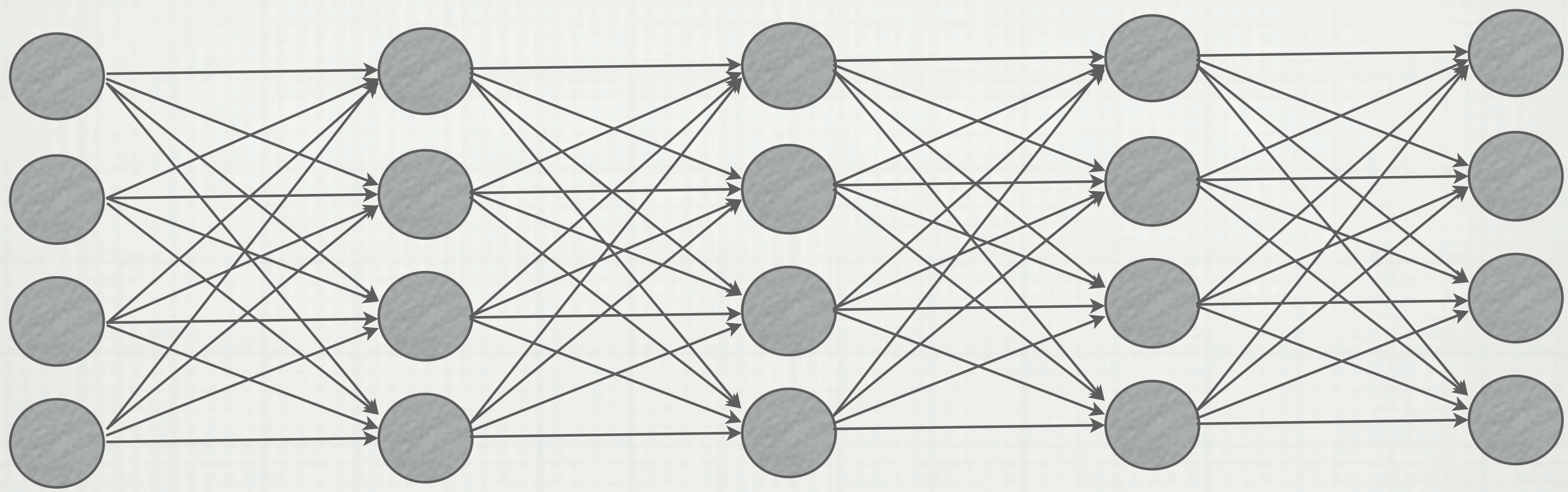
Genes/Interventions Database

Through mid-September 2006, SAGE KE hosted and maintained this database of genes and interventions that have been studied with respect to their effects on life-span or age-related neurological diseases. On 18 September 2006, the Genes/Interventions Database was temporarily shut down. A new version of the database is currently being built and will be hosted at the University of Washington. We will provide information on the new instance of the database on this page when it becomes available.

BROKEN NETWORK MODELS

- START WITH A NETWORK: REAL, RANDOM, OR IDEALIZED
- DEFINE A PROPERTY OF THE STRUCTURE TO BE "FUNCTIONING"
- BREAK EDGES OR REMOVE VERTICES AT SOME RATE
- WHEN DOES THE NETWORK CEASE FUNCTIONING?
- CHAN ET AL. (2004): AGING SCALE-FREE NETWORK MAKES OLDER NODES ISOLATED
- SÖTI AND CSERMELY (2007): WEAK LINK / NETWORK DESTABILIZATION MODEL

CLASSIC VERSION: GAVRILOV SERIES-PARALLEL MODEL



N=5 "ORGANS" WITH K=4 REDUNDANT COMPONENTS.

NETWORK IS DISCONNECTED WHEN SOME ORGAN LOSES ALL COMPONENTS

PLETCHER AND NEUHAUSER (2000) EMBEDDED THIS IN AN EVOLUTIONARY CONTEXT, ALLOWING THE NETWORK STRUCTURE TO EVOLVE

INTERMEDIATE VERSIONS

- BOOLEAN DYNAMICAL SYSTEMS
- WAGNER (1996) MODEL OF GENE-NETWORK DYNAMICS. DISCRETE-TIME DYNAMICS WITH EDGE WEIGHTS. (SEE SIEGAL, PROMISLOW, BERGMAN 2007). SIEGAL, BERGMAN (2002): WADDINGTON'S IDEA OF CANALIZATION AS NETWORK PROPERTY
- AGOSTON ET AL. (2005): PARTIAL WEAKENING OF LINKS, STUDYING EFFECT ON "NETWORK EFFICIENCY" BY SIMULATION ON REAL EMPIRICAL REGULATORY NETWORKS

MUTATION ACCUMULATION MODELS

HOW DO WE EXTEND THIS TO MULTIPLE SITES? KIMURA-MURAYAMA MODEL:

INDIVIDUAL WITH K MUTATIONS HAS FITNESS $(1-S)^K$. EACH NEWBORN GETS EXTRA POISSON(ν) MUTATIONS.

EVOLUTION EQUATION: POPULATION DEFINED AT GENERATION T AS DISTRIBUTION ON NUMBER OF MUTATIONS. THIS IS ALWAYS POISSON WITH MEAN P_T, SATISFYING

$$P_{T+1}=P_T(1-S)+\nu.$$

EQUILIBRIUM WHEN

FREQUENCY OF MUTANT IS ν/S.

HAMILTON (1966): STUDY EVOLUTION OF AGEING BY CONSIDERING "MUTATIONS" THAT RAISE MORTALITY AT ONE AGE.

WHAT IS THE "COST" OF MORTALITY?

SIMPLE MODEL:

COST=LOST FUTURE REPRODUCTION.

DECREASE IN NET REPRODUCTION RATIO (NRR)

$$NRR(g) = \int_0^\infty f_x(g)\ell_x(g)e^{-rx}dx.$$

WHERE $f_x(g)$=FERTILITY AT AGE X,

$\ell_x(g)$=SURVIVORSHIP TO AGE X,

r=POPULATION GROWTH RATE

MUTATION-SELECTION EQUILIBRIUM

INTUITIVE SINGLE-LOCUS MODEL: MUTANT ALLELE ARISES AT RATE V. SELECTIVE COST S.

EQUILIBRIUM WHEN FREQUENCY OF MUTANT IS V/S.

B. CHARLESWORTH (2001):

CONSTANT REPRODUCTION RATE λ

HIGH "BACKGROUND MORTALITY" μ

MUTATION INCREASES MORTALITY BY m AT AGE x

CONSTANT MUTATION RATE V

COST = $\lambda m e^{-\mu x}$ OF TOTAL REPRODUCTION

EXPECT EQUILIBRIUM FREQUENCY $\dfrac{\nu}{m\lambda}e^{\mu x}$

FUNDAMENTAL PROBLEM: MUTATIONS INTERACT

- COST OF MULTIPLE INCREASES TO MORTALITY LESS THAN THE SUM OF INDIVIDUAL COSTS
- THEREFORE PREDICT MORE MUTATIONS THAN LINEAR MODEL
- LINEAR MODEL IS QUALITATIVELY WRONG. MORTALITY RISES PAST EXPONENTIAL, REACHING INFINITY AT FINITE AGE (BEFORE END OF REPRODUCTION)
- GOOD EXAMPLE OF WHERE MORE MATHEMATICS IS NEEDED. SIMPLIFIED MODEL PRODUCES WRONG ANSWER ON ITS OWN TERMS

A DEFENSE OF MATHEMATICS

- MODELS MAY BE TOO COMPLEX. MATHEMATICAL APPROACHES MAY HELP TO SIMPLIFY THEM.
- MODELS MAY BE TOO SIMPLE. MATHEMATICAL APPROACHES MAY HELP TO FIND WHAT ESSENTIAL FEATURES ARE MISSING
- MATHEMATICS MAY EXPLAIN THE MODEL BEHAVIOR

AGE-STRUCTURED POPULATIONS IN RANDOM ENVIRONMENTS

LESLIE MATRIX

$$L = \begin{pmatrix} \mu_0 & \mu_1 & \mu_2 & \cdots & \mu_{\omega-1} & \mu_\omega \\ \lambda_0 & 0 & 0 & \cdots & 0 & 0 \\ 0 & \lambda_1 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & \lambda_\omega & 0 \end{pmatrix} \quad v = \begin{pmatrix} v_0 \\ v_1 \\ \vdots \\ v_\omega \end{pmatrix}$$

V= POPULATION DISTRIBUTION BY AGE CLASS

$V(T)=L^T V(0)$

CONVERGENCE TO STABLE AGE DISTRIBUTION, GIVEN BY TOP EIGENVECTOR.

LONG-TERM POP. GROWTH RATE =TOP EIGENVALUE.

CLUE TO THE "COST" OF CHANGES TO VITAL RATES.

RANDOM ENVIRONMENT ⇒RANDOM LESLIE MATRIX

$$L = \begin{pmatrix} \mu_0 & \mu_1 & \mu_2 & \cdots & \mu_{\omega-1} & \mu_\omega \\ \lambda_0 & 0 & 0 & \cdots & 0 & 0 \\ 0 & \lambda_1 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & \lambda_\omega & 0 \end{pmatrix} \quad v = \begin{pmatrix} v_0 \\ v_1 \\ \vdots \\ v_\omega \end{pmatrix}$$

V= POPULATION DISTRIBUTION BY AGE CLASS

$$V(T) = L^T V(0)$$

AGE DISTRIBUTION DOESN'T CONVERGE

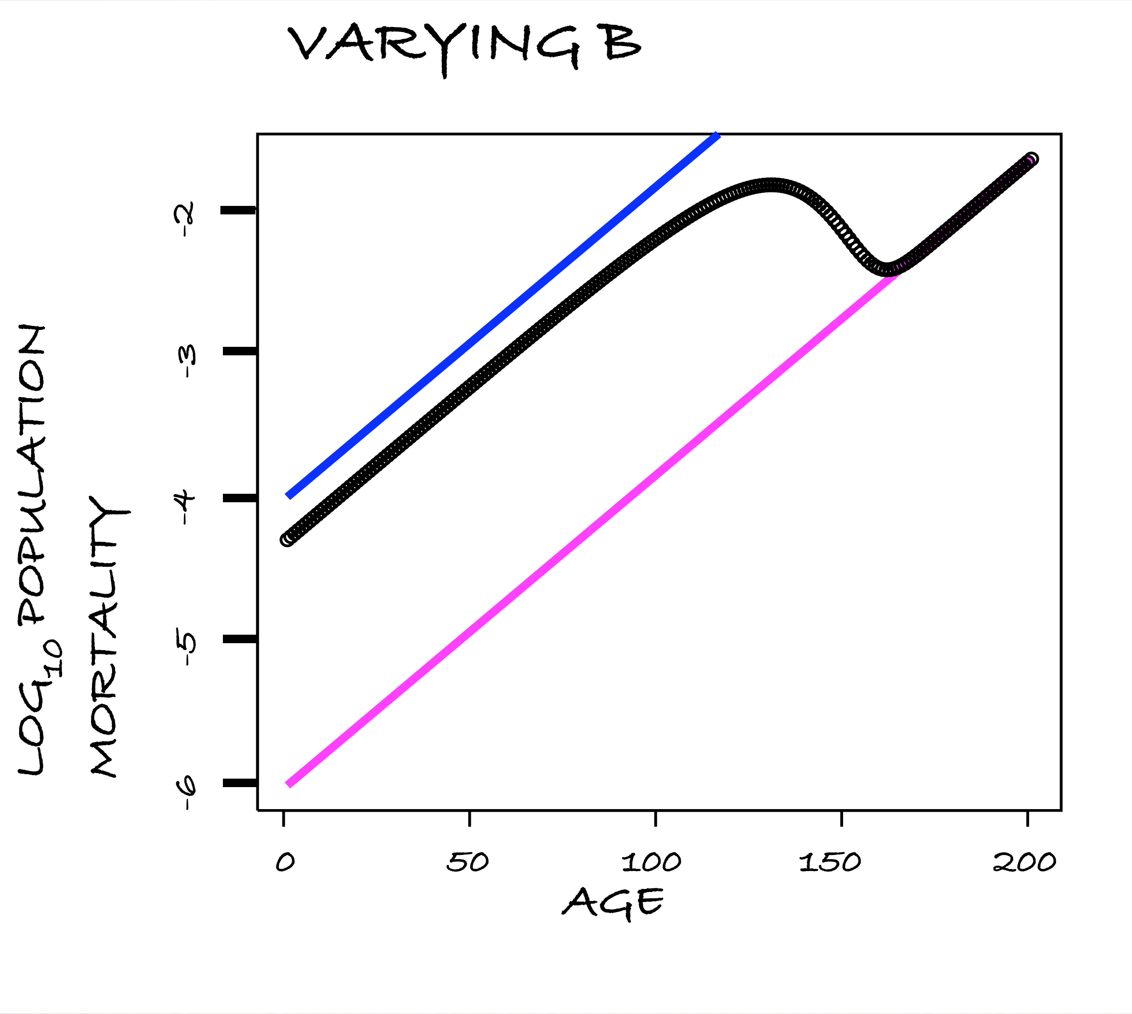
LONG-TERM POP. GROWTH RATE DETERMINISTIC = TOP "LYAPUNOV EXPONENT"

STUDIED FOR PLANT POPULATIONS BY TULJAPURKAR, HORVITZ, PASCARELLA

FIXED FRAILTY (INITIAL HETEROGENEITY) MODEL

FIXED FRAILTY: $\mu_i(x) = B_i e^{\theta_i x}$

EXAMPLE: TWO SUBPOPULATIONS



$B_1 = 10^{-4}$

$B_2 = 10^{-6}$

$\theta = .05$

0 STARTS WITH 50% ROBUST (TYPE 2)

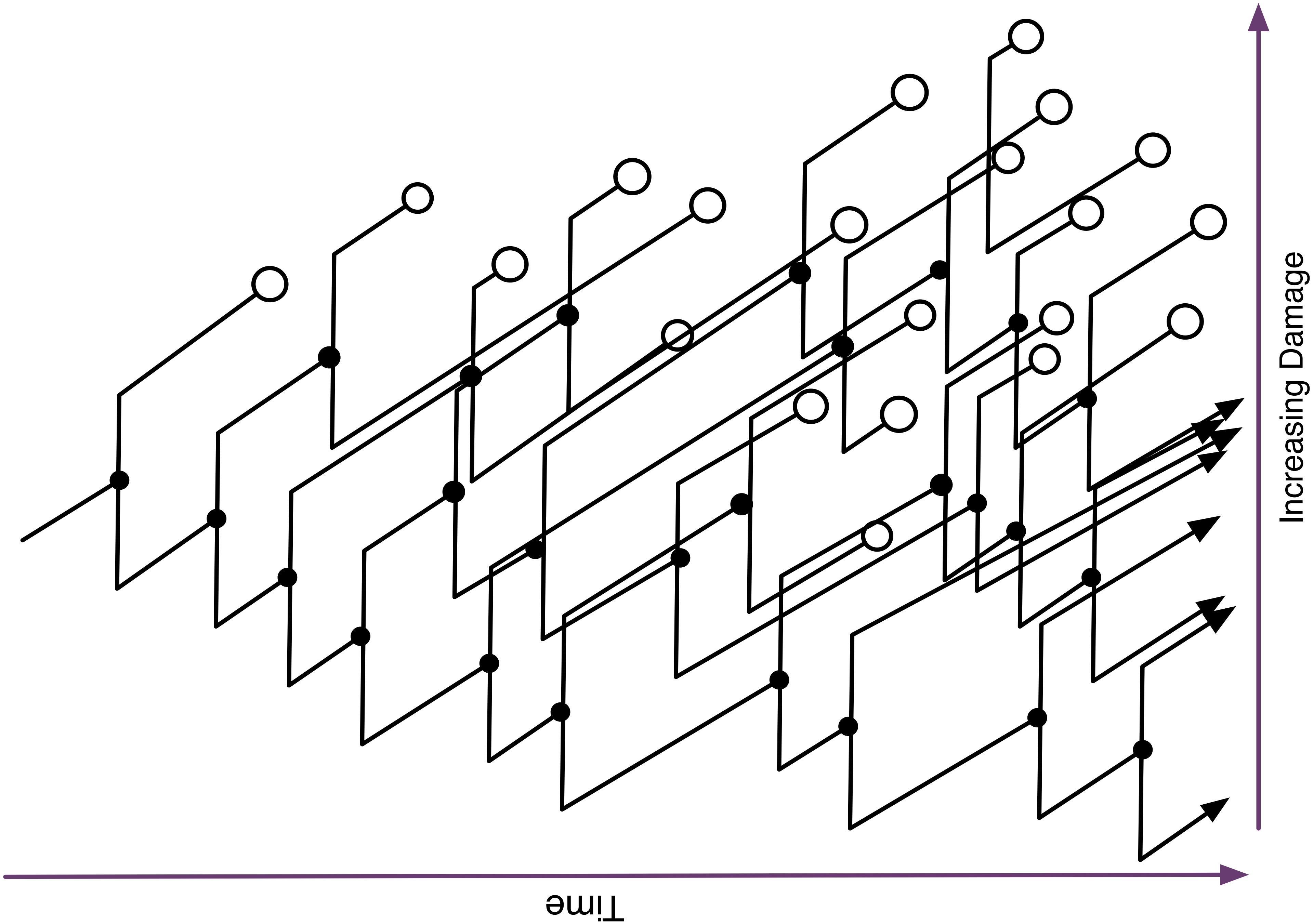
INTRODUCED AS EXPLANATION FOR MORTALITY PLATEAUS BY VAUPEL ET AL., 1979

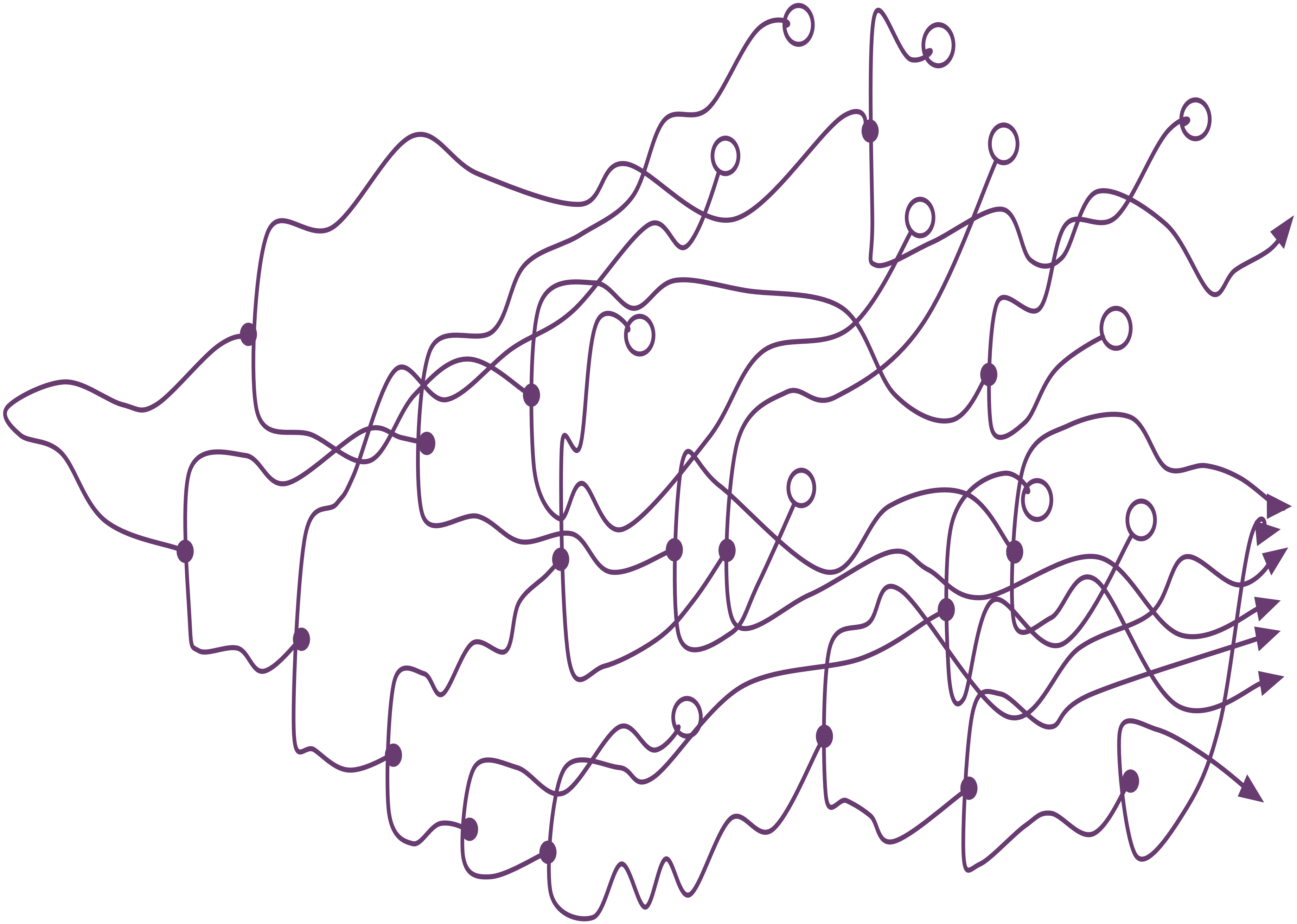
CHANGING FRAILTY MODEL

- OFTEN ABSTRACT SIMPLE MARKOV MODEL OF “VITALITY” OR “SENESCENCE STATE”: LE BRAS (1976), ANDERSON (2000,2009) WEITZ-FRASER (2002)
- COULD ALSO INCORPORATE STOCHASTIC NETWORK MODELS
- GENERICALLY PRODUCES MORTALITY PLATEAUS -- FUNDAMENTALLY STOCHASTIC PHENOMENON
- YASHIN ET AL. (1994) POINTED OUT THAT FIXED- AND CHANGING-FRAILTY MODELS CAN YIELD THE SAME MORTALITY CURVES

DAMAGE ALLOCATION MODELS

- CLASSICAL AGING INVOLVES ASYMMETRIC REPRODUCTION: PARENT RETAINS DAMAGE, PRODUCES PRISTINE OFFSPRING
- PROTOZOANS MAY HAVE ANYTHING BETWEEN PRISTINE OFFSPRING AND SYMMETRIC DIVISION OF DAMAGE
- "AGING" BECOMES A FEATURE OF LINEAGES AND POPULATIONS -- RELATED TO CLASSICAL IDEAS OF MUTATIONAL LOAD, AND BELL'S "EXOGENOUS REPAIR"
- ENCOURAGED BY NEW EXPERIMENTS IN YEAST (<u>LAI ET AL. 2002</u>), CAULOBACTER (<u>ACKERMANN ET AL. 2002</u>), E. COLI (<u>STEWART ET AL. 2005</u>), TRACKING ASYMMETRY


Increasing Damage
Time



- GILLESPIE ET AL. (2004) YEAST ERC'S: SIMULATION, GOAL TO MATCH KNOWN MORTALITY RATES

- WATVE ET AL. (2006 SIMULATION), STEINSALTZ AND EVANS (2007 SUPERPROCESS), ACKERMANN ET AL. (2007 SIMULATION), PAUL (2009 LARGE DEVIATIONS). GOAL: CAN A POPULATION BENEFIT FROM ASYMMETRIC DIVISION OF DAMAGE?

- ANSWER: YES. OPTIMAL POPULATION GROWTH COMES FROM INTERMEDIATE LEVEL OF ASYMMETRY

- DATA-DRIVEN MODELS BY MARSALLE, BANSAYE, OTHERS TO TEST FOR ASYMMETRY IN EXPERIMENTS

GROWTH-REPAIR-REPRODUCTION OPTIMIZATION MODELS

- ONE SORT OF MATHEMATIZATION OF DISPOSABLE SOMA
- MANY VERSIONS: MANGEL, CICHÓN, CHU AND LEE
- OFTEN SOLVED WITH DYNAMIC PROGRAMMING

INTERGENERATIONAL TRANSFER MODEL

- ECONOMISTS AND AN ANTHROPOLOGIST: R. LEE (2003), H. KAPLAN AND A. ROBSON (2002, 2003)

- AGING DRIVEN BY RESOURCE TRANSFERS BETWEEN DIFFERENT AGES: ADULTS INVEST IN CHILDREN

- "CORRECTS" HAMILTON TO SAY THAT MUTATIONS ARE PARTICULARLY SELECTED AGAINST THAT KILLS INDIVIDUAL WHEN NET INVESTMENT IS MAXIMUM

- FASCINATING IDEAS, LEE MODEL SOMEWHAT INCOHERENT