

Control and Optimization of Complex Biological Systems

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Intro to Complex Biological Systems

- Biological systems are characterized by many space and time scales.
- Time scales ranging from milliseconds to years.
- The spatial organization of single molecules can produce the forms of complete organisms, which in turn can organize into spatially complex populations across distances on the order of kilometers.
- Thus, one of the key components in modeling biological systems is to understand not only what the relevant scales are, but also, how to bridge them.

Applying Nonlinear Dynamics to CBS

- Historical Background
 - Nineteenth-century:
 - Non-Euclidean Geometry: space need not be flat
 - Twentieth-century:
 - Relativity: space-time is warped by matter and energy
 - Quantum mechanics: probabilistic; breakdown of causality principle

Chaos

- Random results from simple equations
OR
- Finding order in random results
- Sensitivity to initial conditions
 - Butterfly effect
 - Measurement issues (parameter uncertainty)
- Local randomness vs. global stability
- Deterministic – *not* total disorder

Evolution operator

- Evolution of dynamic system expressed with $x(t) = F^t(\xi)$.
- F^t is evolution operator and translates vector ξ into vector x .
- If dynamic system is linear, it reduces to: $x(t) = F^t \xi$.
- In a discrete space-time regions where the piecewise linear approximation of a dynamic is possible, evolution operator reduces to transfer operator.
- Transfer operator can be described with finite, so called transition matrix.

Evolution operator (cont.)

- In a theory of nonlinear dynamic systems with chaotic behavior eigenvalues of various operators represent certain average values that are globally valid in a whole system.
- e.g. SLEM represents the execution time of a certain computer system, and its minimization shortens computation.
- Eventually, certain CBS can be approached in a same way, thus optimizing its behavior.
- Or even can be brought to a healthy state in a much faster and efficient way than with standard therapeutic protocols.

Calculating Microbes

- Samoyed (pronounced “Sam-oi-ed”), from Wikipedia:
- Is a breed of dog that takes its name from the Samoyedic peoples of Siberia.
- These nomadic reindeer herders bred the fluffy white dogs to help with the herding, and to pull sleds when they moved.
- End of 2010. about seven years old female Samoyed Mini Vini joined her new family.
- She was extremely happy and playfull. →







The Chaos Nightmare

- Unfortunately, and from the beginning, Mini Vini expressed severe UTI symptoms, i.e. pollakiuria, hematuria and cristalliuria.
- *E. coli* and *Staphylococcus* spp. bacteria were found, accompanied with infective struvite stones.
- Several therapeutic cycles with various antibiotics, prescription foods and urine acidifiers followed.
- Begin 2012. Staph. became MRSA, and resistant *Enterococcus* spp. appeared. Stones persisted.
- Mini Vini was deeply distressed and lethargic. →



The Power of Integrative therapy

- Alternative therapeutic approach was urgent.
- Several herbal preparations and homeopathic remedies replaced antibiotics.
- 4 months after starting alternative therapy, urine microbial analysis showed no presence of MRSA and Enterococcus.
- However, E. coli was still there.
- Therefore, antibiotics plus D-Mannose sugar were added to the current therapy.
- Finally, urine was sterile and struvite stones dissolved.

The Complexity of Integrative approach – control parameters

	week 35	week 36	week 37	week 38	week 39	week 40	week 41	week 42
	19/8 - 25/8	26/8 - 1/9	2/9 - 8/9	9/9 - 15/9	16/9 - 22/9	23/9 - 29/9	30/9 - 6/10	7/10 - 13/10
UTI therapy								
Amox/clavulanic acid 250mg					pause	2x1 daily (10 days)		pause
Arctium Lapa SIPF	3x2.5 ml daily		pause	3x2.5ml daily				pause
Basentabletten 125mg	pause	3x2 daily			pause			
Cat's Claw 250mg	2x1 daily			3x1 daily				pause
Cat's Claw 500mg		pause						2x1 daily
Ciprofloxacin 250mg		pause						
Cinnamon 500 mg				2x1 daily				
Cranberry 400mg		pause		2x1 daily		pause	1 x daily	
D-Mannose powder	pause		6 x 2 grams/day	2 x 2 grams/day			pause	
Enrofloxacin 150mg								
Goldenseal 250mg	2x1 daily	pause		2x1 daily	pause	2x1 daily (10 days)	pause	
Herbal tea 1	4 dl daily				pause	4 dl daily	pause	
Herbal tea 2		pause					1 liter daily	
Herbal tea 3		pause			4 dl daily		pause	
Homeopathic remedy 1		pause			2xdaily 5 drops			pause
Homeopathic remedy 2		pause			1xdaily 5 drops			pause
Kidney/Blader caps	2x2 daily					2x3 daily		
N_acetil_L_cisteine 500mg			pause			1/day		pause
Origanum compactum 90mg	pause	3x1 5 days	2x1 9 days	pause	3x1 5 days	2x1 9 days	pause	
Punica granatum 300 mg				2x1 daily				
Uropet DL-Methionine paste					pause			
Uro-Vaxom E. coli extract 6mg	1 x daily 10 days, pause 10 days, 1 x daily 10 days				pause			
Uva Ursi 400mg	pause	3x2 daily			pause			
Vitamin C 250 mg	3x1 daily				pause	2x2 daily		

The Complexity of Integrative approach

- state parameters

- Specific gravity
- ph value
- Leukocytes
- Nitrites
- Proteins
- Blood
- Urine stones
- CFU
- Triglycerides
- ALKP
- etc.

Optimizing Evolution operator of UTI

$F^t =$

	SG	PH	LEU	NIT	PRO	BL	UST	TG	ERY	EC	EF	EFR	S	SR
CFX	x	x	x	x	x	x		x	x	x	x		x	
AMX		x	x	x	x	x			x	x	x		x	
EFX		x	x	x	x	x			x	x	x		x	
SMX		x	x	x	x	x			x	x				
CB			x	x	x	x			x	x				
UT			x		x	x			x		x	x	x	x
AL			x		x	x			x		x	x	x	x
CZ			x	x	x	x			x					
RC			x	x	x	x			x	x				
CF					x	x			x	x				
OC			x	x	x	x			x	x	x	x	x	x
HC			x	x	x	x			x	x	x	x	x	
UU			x	x	x	x			x	x				
PG											x	x	x	x
BP			x		x	x			x	x	x	x	x	x
DM			x	x	x					x				
SD	x					x		x	x					
UX			x	x	x	x			x	x				
RW	x					x	x		x					
HR1	x					x	x		x					
HR2			x	x	x					x	x	x	x	x
UD1	x	x					x							
UD2	x	x					x							
UA	x	x					x							

- Largest Eigenvalue in Magnitude (LEM) of the transition matrix represents the topological entropy of the system.
- Therefore, LEM seems to be a good optimization candidate.

Conclusions and call to action

- Complex biological systems frequently require complex, i.e. integrative therapy approach.
- The complexity of such an approach might prevent clinician to use it.
- Novel methods for coping with this complexity are needed.
- Clinicians, microbiologists, mathematicians and computer experts needs to work closely on solution.
- Nonlinear dynamic approach to this problem deserves further investigation.

