Rocket science & Immuno control dynamics

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Collaboration Team

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It all started with one Melanoma slide

Multi-cellular interaction dynamics Explain telltale signatures

Wanted - New Eyes

Thus, the task is not so much to see what no one yet has seen, but to think what nobody yet has thought about that which everybody sees.

Schopenhauer

With new views

In solving a problem of this sort, the grand thing is to be able to reason backwards. That is a very useful accomplishment, and a very easy one, but people do not practice it much.

> Sherlock Holmes, in Sir Arthur Conan Doyle's A Study in Scarlet

Outline



Successively refining rocket science views

Concepts all apply

None apply as expected

Patient data - Reality

Math analysis - Views

Today – An overview of concepts applied on what, why & how

Immuno control dynamics



Immuno control dynamics observable data

- Patient blood sampling
 - Remote from the Tumor Microenvironment
- Petri-dish Model of Tumor Microenvironment in a Immuno cell/cytokine culture
- Measurements yield population size (counts)
 - Many bio-actions cause population size change
- Data very sparse (time-cost reality limited)
 - Petri-dish: One sample per day
 - Patient: One sample per month
 - One sample = \$150 supplies + 1 lab skilled worker day
- Lots of bio-dynamics going on between sampling

Patient enrolled in trial and pretreatment blood drawn. Patient receives treatment about every 4 weeks with a blood draw prior to each treatment.

Patient has tumor progression, goes off study and has final blood draw.

20 to 50ml of blood comes to the lab for processing.

Sample is spun to separate plasma from white blood cells

Plasma collected, frozen and stored in 1ml aliquots.

Blood concentrations of 42 cytokines are measured in pg/ml.





Blood frequencies of white blood cell types are measured in percentage.



Cellular printed circuitry



Analysis foundation

Aerospace

- Equations known
- Rate of change of momentum=Load
- Given equations, constants & Loads find output
- Compute output & compare to desired output
- Many feedback control analysis tools
 - Link to Immuno-biology
 - Modify to support Immuno control
 - Modify to support emergent behaviour

Immuno-biology

- Equations unknown
- Rate of change of Effect=Cause
- Many observational relationships
- Given relationships + output find Cause
- Assume approximate form for Causal relationships
- Derive associated unknown constants
- Compute output & compare with measured output
- Link to Feedback control tools

Control dynamics problem foundation

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Aerospace

- Newton's equations
- Linear oscillatory
 - Linear signal analysis
- Source springs & dampers
 - Linear springs, dampers
- Conservation of xxx
- Feedback sensors
- Relative position (-) control
- Minimal redundancy
- Minimally adaptable
- Minimal concurrent interaction
- Fragile stability
- Deterministic behaviour

Immuno-biology

- Predator-Prey equations
- Non-linear oscillatory
 - Nonlinear signal analysis
- Sources-Triggers-Modulators
 - Tri-linear springs
- Homeostasis
- Cytokine message carrier
- Population size (x) control
- Massive redundancy
- Massively adaptable
- Massive concurrent interaction
- Robust stability
- Emergent (natural) behaviour

Newtonian equations linearized

 $\frac{dMass*Velocity}{dt} = Spring*Positon + Damper*Velocity$ $\frac{dPosition}{dt} = Velocity$

- Rate of change of momentum = Loads applied
- Linearization yields linear mass spring damper equation
- Position links to velocity by differential relationship
- Response linear harmonic motion

Lotka-Volterra Predator Prey Equations

 $\frac{dFox}{dt} = aFox + bFox * Rabbit$ $\frac{dRabbit}{dt} = cRabbit + dRabbit * Fox$

Foxes reproduce and need survival food

- Rabbits reproduce and need reproduction control
- Interaction dynamics essence lost in linearization
- Used extensively to model bio-system dynamics
- Response non-linear oscillatory with Hopf bifurcation

Computational methods

Finite element theory

- Force-displacement ODEs
- Linear spring
- Visco-elastic force(constant*displacem ent + constant*velocity)
- Model via network of interconnected linear springs
 - CAD model
 - Visualization
- Input mass, spring, damper constants
- Perturb system and predict linear system harmonic response

response ODEs-Ordinary Differential Equations

* New – Specifies all potential Cause-effect relationships

Finite relationship theory*

- Cause-Effect ODEs
- Population growth cause(constant*source*tri gger*modulator) populations
- Model via network of interconnected Uni, Bi & Tri-linear springs
 - Knowledge Model
 - Visualization
- Input observed response
- Predict network constants
- Compute Causal impacts that yield non-linear oscillatory response of observable Effects

Knowledge Model

- Observable Effects impacted by bio-action
- Every bio-action has a Source (Observable Effect)
- Source bio-actions are Triggered (Observable Effect)
- Source bio-actions are Modulated (Observable Effect)
- Bio-actions have many characterization:
 - Secretion, proliferation, recruitment, activation, etc.
 - Modeled as Constant, Uni, Bi or Tri-linear expressions
 - Such expressions are approximations to bio-reality
- Knowledge model collects all such relationships

Causal impact approximation Kolmogorov-Gabor polynomial

- Kolmogorov-Gabor polynomials have been used widely to evolve general non-linear models
 - Heuristic self-organization studies
 - Neural network learning
- All {x's} are known measured observables; e.g. CD3,IL-2,...
- All {u's} are to-be-determined unknowns

$$Y(x_{1}, x_{2}, ..., x_{n}) = u_{0} + \sum_{i} x_{i} u_{i} + \sum_{i} \sum_{j} \sum_{k} x_{i} x_{j} u_{i,j} + \sum_{i} \sum_{j} \sum_{k} x_{i} x_{j} x_{k} u_{i,j,k}$$

Living in the Fast-Lane of the Curse of Dimensionality for Bio Modeling

The Problem:

General Model Formulations Lead to an **Exponential Explosion** in the number of unknowns to be Defined (See Below—NOT GOOD!)

How do we shrink the Problem down to manageable size, while retaining Predictive Power????

 $Y(x_1, x_2, ..., x_n) = u_0 + \sum x_i u_i +$ $\sum_{i}\sum_{j}x_{i}x_{j}u_{i,j} + \sum_{i}\sum_{j}\sum_{k}x_{i}x_{j}x_{k}u_{i,j,k}$

COMMENT: Though Theoretically Valid, If One Insists on Mathematical Purity, You Pay with unrecoverable Computational Difficulties, arising from a Lack of Data for Algorithm Observability. Abandon Algorithm Purity by Invoking Interaction Constraints Defined by Previously Identified **Knowledge Model:** Goal is to Eliminate as many Unknowns as Possible

Original Problem Size

Develop a **Predator - Prey** Based Reverse Engineering Bio-Dynamics Inverse Problem Alg.: Recover Differential Equations, where Coefficients are Derived from Clinical Data

Problem Size after Knowledge Model Invoked

Problem Size after Predator - Prey

Reverse engineering From observations to causes

 E – Effect population (count) is union of all (S) sources, (T) triggers and (M) modulators

 $E = S \cup T \cup M$

- Population changing bio-action Causal impact is sum of all potential components, data defines respective strength of potential contributors
- Insight comes from connectivity between Causal Impacts and predicted Effect response

Dynamics relationship – rate of change of Effect population equal to the sum of all Causal impacts

$$\left\{\frac{dE}{dt}\right\} = \left[S * T * U\right]\left\{u\right\}$$

With observed Effect data & Knowledge model use Singular Value decomposition to compute all values of {u}

With all values of {u} compute all Causal impacts

Proof of concept

Math sanity checks

- Started small Knowledge model just contained the obvious
- Used only basic Knowledge model framework
- Used Math to "see" into Cause & Effect dynamics

Bio sanity checks

- Communicate derived response characterization math views to Immuno-experts
- Explain the unexpected
 - Petri dish test of first anomaly confirmed to be bio-real
- One (to-date) Many random explorations
 - Lots of bio-variability overlays patient agnostic response patterns
 - Need to expose patient agnostic response patterns

Extending software to accommodate ALL potential connectivity

- Let the data find the ignorable
- Let the data find the analysis path to Clinical relevance

Examples of Raw data

Raw data PD-noVEGF CD11c.14



Raw data LK-76 CD11c.14



Raw data PD-noVEGF IL-10





Influence (Causal impact) arrays Petri dish vs. Patient

	PD-VEGF				м	0	D	U	L	A	Т	0	R	S				
	CD11c.14			GM-CSF	GRO	IL-1b	IL-2	IL-8	IL-13	IP-10	MCP-1	MIP-1a	MIP-1b	RANTES	sCD40L	sIL-2Ra	TNFa	TNFb
	CD11c.14	12.50	84.26	8.41	2.52	3.23	4.21	11.74	2.84	5.70	11.16	12.82	21.79	7.08	34.80	27.98	6.17	20.03
	IL-10	1.00	1.96	0.35	0.47	0.80	1.65	4.59	0.06	1.66	4.71	5.01	7.05	3.86	2.17	0.21	2.42	0.09
	GM-CSF	0.60	3.38	0.43	0.27	0.46	0.95	2.66	0.07	0.98	2.73	2.90	4.17	2.24	1.27	0.27	1.40	0.10
	GRO	0.41	7.60	0.88	0.19	0.32	0.66	1.84	0.15	0.68	1.89	2.01	2.88	1.55	0.88	0.54	0.97	0.21
	IL-1b	1.46	24.42	1.31	0.29	0.41	0.46	1.28	0.22	1.79	1.31	1.40	7.64	1.18	2.01	0.81	0.67	0.30
	IL-2	1.17	21.15	0.64	0.21	0.41	0.26	0.74	0.08	1.41	0.02	0.81	5.93	0.70	1.55	0.12	0.39	0.07
F	IL-8	1.17	21.15	0.64	0.21	0.41	0.26	0.74	0.08	1.41	0.02	0.81	5.93	0.70	1.55	0.12	0.39	0.07
	IL-13	0.73	2.83	0.49	0.21	0.34	0.71	1.99	0.07	0.76	2.04	2.17	3.62	1.69	1.00	0.21	1.05	0.14
С	IP-10	0.90	2.11	0.29	0.42	0.73	1.49	4.16	0.02	1.49	4.26	4.54	6.33	3.49	1.95	0.09	2.19	0.07
Г	MCP-1	0.92	17.49	0.51	0.15	0.37	0.36	1.00	0.08	1.08	1.02	1.09	4.53	0.83	1.18	0.29	0.53	0.11
s	MIP-1a	1.17	21.15	0.64	0.21	0.41	0.26	0.74	0.08	1.41	0.02	0.81	5.93	0.70	1.55	0.12	0.39	0.07
	MIP-1b	0.64	3.22	0.40	0.29	0.49	1.02	2.85	0.06	1.05	2.92	3.11	4.48	2.41	1.37	0.15	1.50	0.11
	RANTES	0.67	13.85	0.37	0.16	0.33	0.57	1.60	0.05	0.76	1.64	1.74	3.13	1.34	0.81	0.07	0.84	0.04
	sCD40L	0.80	4.26	1.80	0.38	0.64	1.32	3.69	0.31	1.32	3.78	4.03	5.61	3.10	1.73	1.10	1.94	0.41
	sIL-2Ra	1.50	4.64	1.02	0.30	0.24	0.61	1.71	0.14	1.57	1.87	1.87	7.47	1.94	2.05	0.39	0.90	0.29
	TNFa	1.17	21.15	0.64	0.21	0.41	0.26	0.74	0.08	1.41	0.02	0.81	5.93	0.70	1.55	0.12	0.39	0.07
	TNFb	1.37	5.24	1.09	0.28	0.29	0.62	1.75	0.18	1.43	1.80	1.91	6.80	1.77	1.87	0.67	0.92	0.26

	LK-28				м	о	D	U		L	А		т	0	R	s						
	CD11c.14	IL-10	VEGF	G	M-CSF	GRO	IL-1b	IL-2	IL-8	IL-1	3	IP-10	м	ICP-1	MIP-1a	MIP-1b	RANTES	sCD40L	sIL-2Ra	TNFa	TNFb	
	CD11c.14	().15	0.41	0.1	15.8	8 0.08	C		4.57	3.79	3	7.39	3.97	0.0	0.2 0.2	<mark>6</mark>	0 45.45	5	0	0	1.27
	GM-CSF	C	0.01	0.04	0.02	0.	2 <mark>0.01</mark>	C	כ	0.29	0.02		1.97	2.49	0.3	81 0.9	<mark>8</mark>	0 16.7	7	0	0	0.01
	GRO		0	0.01	C	0.0	1 0	C	o <u> </u>	0.04	0		0.14	0.16	0.0	0.0	3	0 7.89	9	0	0	0
	IL-10		0	0.02	0.01	0.0	9 0.01	C	0	0.14	0.01		0.93	1.18	0.1	.5 0.4	<mark>7</mark>	0 7.92	2	0	0	0.01
Е	IL-13		0	0.01	C	0.0	<u>1</u> 0	(o <u> </u>	0.02	0		0.14	0.17	0.0	0.0	7	0 7.62	2	0	0	0
F	IL-1b	C).01	0.04	0.03	0.	2 <mark>0.01</mark>	(ו	0.3	0.02		2.04	2.59	0.3	3 <mark>2 1.0</mark>	2	0 17.35	5	0	0	0.01
F	IL-2		0	0	C	0.0	<u>1</u> 0	(o <u> </u>	0.04	0		0.09	0.12	0.0	0.0	5	0 3.69	9	0	0	0
E	IL-8	().01	0.04	0.03	0.	2 0.01	(0.3	0.02		2.04	2.58	0.3	32 1.0	2	0 17.32		0	0	0.01
с	IP-10	().01	0.04	0.02	0.1	8 0.01	(0.27	0.02		1.85	2.35	0.2	9 0.9	<mark>3</mark>	0 15.72		0	0	0.01
т	MCP-1	().01	0.04	0.03	0.	2 0.01	(0.3	0.02		2.01	2.55	0.3	32 1.0	1	0 17.1		0	0	0.01
s	MIP-1a	().01	0.04	0.03	0.2	1 0.01	(0.32	0.02		2.15	2.73	0.3	4 1.0	8	0 18.27	,	0	0	0.01
	MIP-1b	(0.01	0.04	0.03	0.2	1 0.01	(0	0.32	0.02		2.13	2.7	0.3	34 1.0	7	0 18.13		0	0	0.01
	RANTES		0	0	C		o c	(C	0	0		0	0		0	0	0 0)	0	0	0
	sCD40L		0	0	C		o c	(C	0	0		0	0		0	0	0 ()	0	0	0
	sIL-2Ra		0	0	C		<u>)</u> a	(<u></u> د	0	0		0	0		0	<u>o</u>	0 <u> </u>	<u>)</u>	0	0	0
	TNFa	().01	0.04	0.02	0.	2 0.01	(2	0.29	0.02		1.98	2.51	0.3	s1 0.9	9	0 16.84		0	0	0.01
	TNFb		0	0	C	0.0	1 0	C	C	0.01	0		0.07	0.08	0.0	01 0.0	2	<mark>0</mark> 4.1		0	0	0

Causal Impact analysis detail (example)



Positive values imply cytokine secretion Negative values imply cytokine absorption

Statistical analysis mean & variance

Strong & Weak contributors

- Modulators that impact cellular population change
- Causal impact mean
 & variance values across all patients
 and views

		Mean			Variance				
	CD11c.14	CD4.294(Th2)	CD4.TIM3(Th1)	CD11c.14	CD4.294(Th2)	D4.294(Th2) CD4.TIM3(Th1)			
EGF	0.56	0.44	0.48	0.68	0.30	0.40			
EOTAXIN	1.47	1.44	1.81	6.22	5.82	9.34			
FGF-2	0.05	0.03	0.03	0.01	0.00	0.00			
FRACTALINE	0.05	0.04	0.03	0.00	0.00	0.00			
G-CSF	0.05	0.03	0.05	0.01	0.00	0.01			
GM-CSF	0.13	0.13	0.14	0.03	0.05	0.03			
GRO	1.45	1.43	1.55	2.16	2.88	2.57			
IFNa2	0.08	0.07	0.07	0.02	0.01	0.01			
IFNg	0.01	0.01	0.01	0.00	0.00	0.00			
IL-10	0.00	0.00	0.00	0.00	0.00	0.00			
IL-12p70	0.01	0.01	0.01	0.00	0.00	0.00			
IL-13	0.07	0.03	0.01	0.03	0.01	0.00			
IL-15	0.02	0.02	0.02	0.00	0.00	0.00			
IL-17	0.04	0.04	0.04	0.01	0.01	0.01			
IL-1a	0.38	0.19	0.18	0.74	0.09	0.08			
IL-1b	0.06	0.06	0.06	0.00	0.00	0.00			
IL-2	0.00	0.00	0.00	0.00	0.00	0.00			
IL-3	0.00	0.00	0.00	0.00	0.00	0.00			
IL-4	0.04	0.02	0.03	0.01	0.00	0.00			
IL-5	0.00	0.00	0.00	0.00	0.00	0.00			
IL-6	0.08	0.08	0.09	0.01	0.01	0.01			
IL-7	0.00	0.00	0.00	0.00	0.00	0.00			
IL-8	2.24	2.54	2.40	10.64	15.72	11.79			
IL-9	0.00	0.00	0.00	0.00	0.00	0.00			
IP-10	1.52	1.23	0.90	2.11	0.89	0.50			
MCP-1	1.25	1.16	1.01	1.72	1.02	0.57			
MCP-3	0.03	0.02	0.02	0.00	0.00	0.00			
MDC	1.78	1.57	1.84	4.16	3.30	4.58			
MIP-1a	1.17	0.81	1.05	2.58	0.81	2.32			
MIP-1b	0.60	0.60	0.50	0.45	0.32	0.18			
PDGF-AA	2.09	1.99	2.87	6.12	4.48	7.41			
PDGF-AA/AB	2.93	3.42	4.19	16.04	18.96	15.54			
RANTES	4.97	5.00	6.33	11.67	15.59	18.24			
sCD40L	3.79	3.70	4.53	5.99	6.70	8.58			
sIL-2Ra	0.30	0.38	0.31	0.10	0.15	0.13			
TGFa	0.01	0.02	0.02	0.01	0.03	0.02			
TNFa	0.07	0.02	0.04	0.14	0.01	0.01			
TNFb	0.07	0.04	0.04	0.16	0.04	0.02			
VEGE	0.20	0.22	0.20	0.02	0.02	0.01			





Examples of Non-linear Rhythmic Synchronicity

Statistical analysis Pearson correlation coefficients

- The Pearson correlation coefficient, is sensitive only to a linear relationship between two variables. Other measures exist for the non-linear relations.
- By computing the Pearson correlation coefficient with a signal and a delayed signal we can extract a delayed linear relationship; i.e. Cytokine communication response X-talk.
- Example (next slide): Pearson correlation coefficients show the degree that Cellular CD11c.14, CD4.294(Th2) and CD4.TIM3(Th1) growth modulators work together.
 - The statistics spans all patients, all cellular modulation growth views and all associated growth inducing bio-actions.
 - Highlighted are correlations greater than .75

Cytokine X-talk relationship strength & the Modulation of Cellular growth

CD11c.14	EGF	EDTAXIN	GM-CSF	GRO	ITNa2	IL-1a	11-6	1-8 17-10		MCP-1	MDC	MP-1a	MIP-15 POOF-AA		POGF-AA/AB RANTES sCD40L		CD40L	siL-2Ra	VEGF
EGF	1.00																		
EDTAXIN	-0.63	1.00	1.00																
GRO	0.44	-0.32	-0.32	1.00															
IFNa2	0.42	-0.42	0.59	-0.44	1.00								Value > .75						
IL-1a	0.76	-0.50	0.22	-0.15	0.89	1.00													
IL-6	-0.26	-0.07	0.00	-0.45	0.19	0.10	1.00												
10.10	0.21	-0.17	-0.35	0.94	-0.65	-0.40	-0.47	1.00	1.00										
MCP-1	-0.15	0.49	-0.58	0.56	-0.86	-0.67	-0.59	0.71	-0.16	1.00									
MDC	0.15	0.62	-0.69	0.09	-0.31	-0.06	-0.36	0.06	0.39	0.59	1.00								
MIP-1a	-0.43	0.44	-0.30	-0.40	-0.15	-0.16	0.79	-0.38	-0.16	-0.16	0.15	1.00							
MIP-16	-0.07	0.10	-0.43	0.79	-0.71	-0.50	-0.05	0.81	-0.12	0.64	0.14	0.17	1.00						
POGF-AA	-0.13	0.66	-0.57	0.06	-0.48	-0.36	-0.41	0.07	-0.01	0.66	0.88	0.13	0.19	1.00	1.00				
BANTES	-0.37	0.20	0.12	0.35	-0.33	-0.45	-0.31	0.31	-0.41	0.39	0.07	-0.16	0.01	0.41	0.38	1.00			
sCD40L	-0.15	0.16	-0.26	0.69	-0.67	-0.58	-0.38	0.68	-0.29	0.69	0.24	-0.06	0.80	0.51	0.42	0.82	1.00		
slL-28a	-0.13	-0.33	0.44	0.53	-0.17	-0.33	-0.32	0.52	-0.42	0.17	-0.47	-0.52	0.39	-0.20	0.67	0.74	0.59	1.00	
VEGF	0.37	-0.29	-0.54	0.86	-0.62	-0.31	-0.48	0.87	0.06	0.65	0.18	-0.35	0.65	0.24	-0.19	0.20	0.66	0.32	1.00
CD4.294(Th2)	EGF	EDTAXIN	6M-CSF	GRO	IFNa2	IL-1a	IL-6	18	IP-10	MCP-1	MDC	MIP-1a	MIP-15	PDGF-AA	PDGF-AA/AB	RANTES 5	CD40L	stL-2Ra	VEGF
EGF	1.00	1.00																	
GMCSE	-0.73	-0.18	1.00																
GRO	0.72	-0.11	-0.47	1.00															
IFNa2	-0.77	-0.20	0.93	-0.73	1.00														
IL-1a	0.01	-0.49	0.19	-0.49	0.45	1.00							Value > .75						
IL-6	-0.25	0.25	-0.22	0.02	-0.22	-0.30	1.00												
12.10	0.75	-0.11	-0.46	0.97	-0.71	-0.37	0.00	1.00	1.00										
MCP-1	0.47	0.57	-0.69	0.49	-0.75	-0.37	-0.09	0.47	0.70	1.00									
MDC	0.36	0.71	-0.72	0.33	-0.72	-0.49	-0.02	0.30	0.48	0.88	1.00								
MIP-1a	-0.51	0.53	-0.16	-0.45	0.00	-0.09	0.63	-0.51	0.06	0.17	0.19	1.00							
MIP-15	0.56	-0.01	-0.A7	0.92	-0.69	-0.45	0.34	0.90	0.38	0.43	0.28	-0.20	1.00						
POGE-AA/AB	-0.43	-0.13	-0.46	0.07	-0.42	-0.32	-0.20	-0.05	-0.55	-0.21	-0.39	-0.06	0.08	-0.18	1.00				
RANTES	0.18	-0.13	0.08	0.65	-0.14	-0.29	-0.04	0.57	-0.08	0.17	-0.02	-0.27	0.70	0.02	0.67	1.00			
sCD40L	0.60	0.00	-0.46	0.90	-0.69	-0.46	-0.01	0.82	0.40	0.65	0.39	-0.17	0.84	0.25	0.26	0.74	1.00		
siL-28a	0.43	-0.30	0.04	0.84	-0.27	-0.42	-0.20	0.79	-0.08	0.12	-0.03	-0.65	0.73	-0.17	0.49	0.83	0.74	1.00	
VEGF	0.92	-0.23	-0.75	0.85	-0.87	-0.34	-0.07	0.80	0.43	0.52	0.45	-0.39	0.70	0.11	-0.27	0.32	0.75	0.56	1.00
CD4.TIM3(Th1)	EGF	EDTAXIN	GM-CSF	GRO	ITNa2	IL-1a	IL-6	1.4	IP-10	MCP-1	MDC	MIP-1a	MIP-15	PDGF-AA	PDGF-AA/AB	NANTES 6	CD40L	siL-2Ra	VEGF
FOTAXIN	0.19	1.02																	
GM-CSF	-0.87	-0.19	1.00																
GRO	0.79	-0.15	-0.54	1.00															
IFNa2	-0.68	0.38	0.61	-0.62	1.00														
IL-1a	0.52	0.74	-0.50	0.28	0.25	1.00							Value > .75						
IL-6	0.00	0.22	-0.10	-0.08	0.50	0.59	1.00	1.00											
12-10	0.64	-0.11	-0.58	0.87	-0.78	-0.07	-0.09	1.00	1.00										
MCP-1	0.87	0.38	-0.75	0.78	-0.63	0.39	-0.31	0.63	0.85	1.00									
MDC	0.66	0.82	-0.71	0.52	-0.16	0.71	0.04	0.23	0.85	0.80	1.00								
MIP-1a	-0.17	0.21	0.00	-0.32	0.65	0.52	0.95	-0.61	-0.27	-0.42	-0.02	1.00							
MIP-1b	0.45	-0.25	-0.21	0.90	-0.61	-0.13	-0.07	0.90	0.50	0.33	-0.01	-0.35	1.00	1.00					
PDGE-AA/AP	0.04	0.01	-0.62	0.39	0.32	0.46	0.04	-0.01	0.12	0.04	0.04	-0.28	0.05	0.28	1.00				
RANTES	0.25	0.25	-0.04	0.58	-0.13	0.13	-0.25	0.38	0.52	0.42	0.34	-0.31	0.39	0.61	0.74	1.00			
sCD40L	0.72	0.31	-0.47	0.93	-0.37	0.46	0.08	0.66	0.81	0.72	0.57	-0.11	0.64	0.67	0.51	0.74	1.00		
siL-2Ra	-0.27	-0.36	0.49	0.34	-0.15	-0.61	-0.31	0.45	0.02	-0.12	-0.40	-0.41	0.62	-0.15	0.60	0.48	0.28	1.00	
VEGF	0.77	-0.29	-0.61	0.80	-0.94	-0.12	-0.35	0.85	0.57	0.73	0.25	-0.58	0.71	0.41	-0.08	0.24	0.59	0.25	1.00

Reference: Thirteen ways to look at the correlation coefficient by J.L. Rodgers and W.A. Nicewander

Pearson Correlation Coefficients

- Show Synchronicity wiring diagrams
- Show Orthogonality of Effect (measured) vs. Effect (computed per Causal Impact)
- Orthogonality implies long term damping
- Feeding off of very small nutation instability studies; e.g., thermally induced instabilities
 - Identify the negative damping cause
 - Looks promising but not yet there

Bio-observable Synchronicity wiring-diagrams

> Examples of Patient Bio-variability







Control dynamics

Aerospace

- Continuous or discrete error signal generated
- Requires the math operation of "subtraction"
 - Error equals desired minus actual
- Control system commands action that will drive observed error signal to zero
- Active control ends when error signal stops
- Adaptive control founded on
 - Parameter estimation

Immuno control

- No concept of "error signal"
- No Math operation of "subtraction"
- Has "decision making" measures
 - Self-organization
 - Start/end task
- Has Logistics subsystem
 - Manages flow of mass, energy and signaling resources to meet Immuno control needs
- Control parameters undefined
- Control subsystems interwoven

Feedback control vs. Process decision making

Aerospace

- Mode control
 - Well defined rules
- Feedback control
 - Well defined error and command signals
- Linear process with nonlinear contributions

Immuno-biology

- Bio-action event control
 - Patient variability
 - Many concepts support decision making process
 - Swarm intelligence"
 - Ants, honeybees, locusts, termites, birds, fish, etc.
- Bio-chemical process
 - Rules unclear
 - Parameters unclear
 - Extensive networking
 - Multi-use & redundancy
- Foundationally non-linear process

Decision making signal detection & duration

- Linear elector-mechanical systems
- Addition and subtraction of linear signals
 - Comparable strength
- Many data samples per highest frequency of importance

- Non-linear bio-system
- Addition and subtraction of nonlinear (triple-product) signals
 - Significant amplification above linear signal strength
 - Maybe: Re. coarse data
 - Via DNA rules and triple products amplify/suppress essence of sensed data
 - Self-organization concept
- Maybe: Re. Limited memory duration
 - process focused within a sliding window of relevance.

Swarm intelligence & Modes bio-action

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Ants



Termites





Self-organization

Chemotaxis (Search & destroy)

- Diversity of knowledge
 - Robust decision making (Bioaction event triggering)
 - Indirect collaboration
 - Timely reaction of bio-action event sources to invasion
 - Adaptive mimicking
 - Massive coordination of Immuno defense options
- Dark side
 - Immuno defense destabilization

http://rallythecause.com/2011/12/19/quotes -and-ideas-from-the-smart-swarm/

Cellular decision making & "Honeybee Democracy"*

Cells have many bio-functions

- Bio-function action level requires decision making
- Microenvironment is probed
- Observable (unknown) decision making parameters are reported to cellular receptors
 - Pathways from receptors to nucleus for data processing exist
- Causal impact data reveals response consistent with low level probing ending with bio-action
- Swarm intelligence & emergent behavior

- Honeybee colonies perform many tasks
- Honeybee task performance requires decision making
- Near nest environment is probed
- Observable decision making parameters are reported to colony via "dance"
- Consensus based decision is made and acted upon
- Swarm intelligence & emergent behavior

* Title of book by Thomas D. Seeley

Task scheduling in Immuno control dynamics

Task control concept thoughts:

- Task is triggered
- Task is maintained
- Task is stopped

Logistics control

- Supports task activity
- Delivers to task source
 - Energy packets
 - Construction material
 - Activity control signals
- Delivers task source products to
 - Task's support target micro-environment

Decision making for

- Task triggering
- Task stopping
- Logistics required for
 - Task maintenance
 - Gathers and delivers task maintenance necessities to activity micro-environment
 - Delivers products of task to Logistic subsystem for distribution and delivery
- Task activity
 - Well scripted sequences of (resource limited) biochemical actions and reactions

Immuno-control breakdown

- Via Causal impacts discover organizational hierarchy
 - Organizational groups are networked
- Via Bio-expert knowledge base + Causal impact data
 - Infer Immuno-control system breakdown and networking
 - Identify potential points for clinical intervention
- Via correlation & statistical analysis
 - Identify key enablers of tasks
 - Identify natural behaviors and participants
 - Link tasks with enablers
 - Associate to clinical relevance

Physical cosmology and Quantum mechanics Searching for ideas to borrow

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- Remove observed all sky mapping background, what happens long term
- Quantum information and computation
- Variables of state position, spin, momentum
- Searching for bio-matter need to reflect "Size" relative to:
 - production & absorption
 - stimulation & suppression
- Searching for generic rules that cross patient bio-variability

- Remove short term transient Immuno response, what happens long term
- Immuno communication via concentration gradients & neural computation
 - Beyond binary logic
- Variables of state populations of effect, source, trigger, modulator
- Can't get to certainty
 - Massively: robust, redundant and adaptable
- Synchronicity & self-organization

Very new - Physical Cosmology Dark Matter-Energy vs. Dark bio-stuff gradients



Multi Spectral imaging







Proposal submitted by Midwest Melanoma Partnership

- Clinical trial 30 patients with metastatic melanoma
- Ipilimumab (IPI) Immunotherapy treatment for 12 weeks
 - Treatment on weeks 1,3,6,9: Blood drawn weekly
 - Tumor biopsies & imaging on weeks 1,6,12
- All data to be used to reverse engineer Immuno control dynamics in Tumor microenvironment (TME)
 - Compare analysis results across all patients
 - Identify statistically meaningful correlations between all Effects measured and all population changing Causal impacts
 - Perform focused experimental validation Petri dish tests
 - Perform Clinical validation of new understandings
 - Apply Cause-effect understanding of IPI & patient's Immuno control dynamics response within the TME

Patience + Understanding = Progress







Patience + Understanding = Progress

