A Systems Approach to Schizophrenia

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Schizophrenia fact sheet

- Major mental disorder, affecting cognitive, emotional and motivational aspects of behavior;
- relatively common (1.1%, over 2.2 mill. in the US each year);
- devastating impact on social functioning: associated with homelessness, suicide, unemployment, substance abuse;
- structurally and functionally affects cortical and subcortical regions;
- complex and widespread symptoms:

NEGATIVE SYMPTOMS				
SPEECH poor content or quality	AFFECT flatness withdrawal	VOLITION negativism ambivalence obedience	CATATONIA mannerism posturing stereotypes	PSYCHOLOGICAL impaired attention, intelligence, memory, perception
POSITIVE SYMPTOMS				
HALLUCIANTIONS=*distortions of a real perceptual experience:* perception without object misrecognition broadcast thoughts and voices external force control		DELUSIONS=*impossible beliefs held with conviction and certainty, impervious to counterargument:* persecutory, referential, religious, grandiose		
OTHERS: depreciation of sense of time and space, other bizarre behavior				

- unknown causes and neuro-physiological mechanisms;
- consensual axiomatic definition, published periodically in DSM;
- diagnosis based on statistical behavior rather than etiology;
- symptomatic components overlap with those of other conditions;
- currently incurable, as all treatment remains elusive .

Limbic dysregulation hypothesis

The etiology of schizophrenia is based on neural vulnerability and degeneration. The symptoms eventually result as an overlap of environmental stress onto the individual's hereditary premorbid predisposition. Schizophrenia is an end-stage of a cyclic neurodegenerative process, in which certain negative feed-back loops that govern brain interactions are broken:

Pre-existing hippocampal/prefrontal deficit

↓

Decreased inhibition of the amygdala

↓

Higher arousal levels, even under minor stress

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Autonomic and endocrine effects
(changes in HRV, electrodermal activity, cortisol levels)

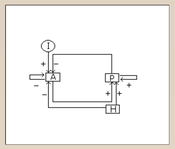
↓

Brain neurotoxicity

↓

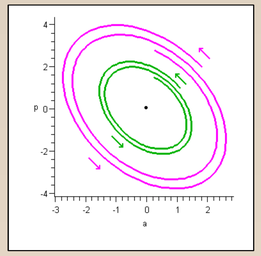
Further hippocampus/prefrontal damage

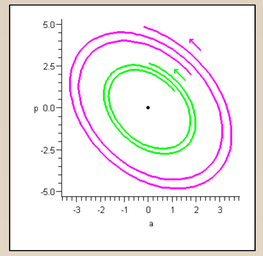
Linear model:



$$\frac{da}{dt} = -\mu_1 a - k_1 p + I - \gamma_1 H$$

$$\frac{dp}{dt} = k_2 a + \mu_2 p + \gamma_2 H$$





Fixed point at:

$$(a^*, p^*) = \left(\frac{k_2 I + H(\mu_1 \gamma_2 - \gamma_1 k_2)}{\Delta}, \frac{-\mu_1 I + H(\gamma_1 \mu_2 - k_1 \gamma_2)}{\Delta} \right)$$

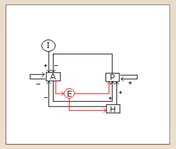
where $\Delta = k_1 k_2 - \mu_1 \mu_2$ is the determinant of the system's Jacobian matrix.

Suppose that $\Delta = k_1 k_2 - \mu_1 \mu_2 > 0$.

- If $\mu_1 > \mu_2$ then (a^*, p^*) is a global attractor
- If $\mu_1 < \mu_2$ then (a^*, p^*) is a global repeller.

Interpretation: The system converges to an equilibrium as long as the amygdala self-inhibition is strong enough to exceed the prefrontal self-excitation. Otherwise, the trajectories are repelled away from the equilibrium. It is unlikely that the brain operates with such on-off switches between stable and unstable behaviour. A linear model is therefore too simplistic to capture more subtle phenomena.

Nonlinear model:



$$\frac{da}{dt} = -\mu_1 a - k_1 p + I - \gamma_1 [H - \gamma(a - a^*)]$$

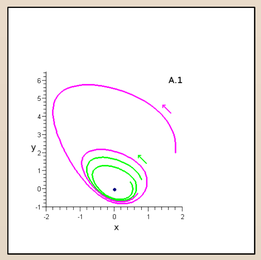
$$\frac{dp}{dt} = k_2 a + \mu_2 p + \gamma_2 [H - \gamma(a - a^*) + \delta(a - a^*)(p - p^*)]$$

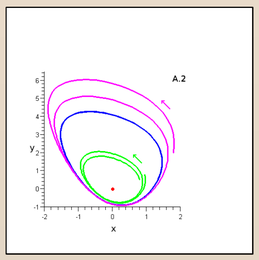
The system has a fixed point at (a^*, p^*) and exhibits a Hopf bifurcation at $\mu_1 = \mu_2$, with Lyapunov number:

$$\sigma = \frac{3\pi}{2\gamma\gamma_1 \Delta^{3/2}} (\delta\gamma_2 + 2\gamma\gamma_1)[\mu_2(\delta\gamma_2 - \gamma\gamma_1) + k_1\gamma_2\gamma]$$

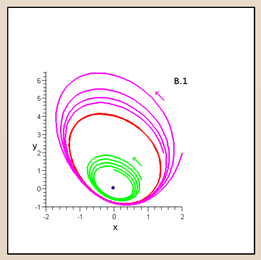
Interpretation:

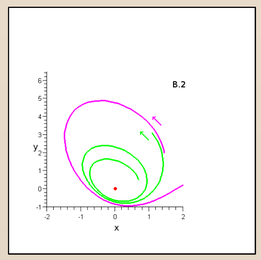
- $\sigma > 0$ corresponds to healthy limbic regulation. An overactive amygdala won't prevent the trajectories form eventually stabilizing, but can force them to stabilize to a regime of wider oscillations.
- $\sigma < 0$ is the signature of schizophrenia. If a stimulus elevates amygdala activation to a value outside of the attraction basin, the trajectory will perform larger and larger oscillations, corresponding to the psychotic behaviour observed in schizophrenic patients.





- If $\sigma > 0$, the system has a subcritical Hopf bifurcation at $\mu_1 = \mu_2$.
  - For $\mu_1 > \mu_2$, (a^*, p^*) is an attractor.
  - For $\mu_1 < \mu_2$, (a^*, p^*) is a repeller surrounded by an attracting cycle.





- If $\sigma < 0$, the system has a supercritical Hopf bifurcation at $\mu_1 = \mu_2$.
  - For $\mu_1 > \mu_2$, (a^*, p^*) is an attractor surrounded by a repelling cycle.
  - For $\mu_1 < \mu_2$, (a^*, p^*) is a repeller.

Conclusions:

Two clinical systems with very similar underlying rules can exhibit drastically different long term behaviour when started under the same initial conditions. A bifurcation could constitute the normality versus pathology threshold needed for clinical evaluations. Then, both diagnosis of illness and quantification of illness severity could be achieved by calculating the Lyapunov number of a system constructed from clinical measures. Our model supports the idea that the dynamics of a diseased system is not driven randomly, but is rather only apparently random due to its complicated behaviour over short time periods. This idea is very important for clinical treatment, as the behaviour of a deterministic system can be changed by proper tuning of the parameters.