Mechanisms and Manipulability in Neuroscience:

From Component Activities to System Behaviour by *Bottom-up* Causation

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Abstract

Many physical mechanisms are in good approximation described by finite-state probabilistic or deterministic models. For such models the relationship component activity to system behaviour, controversial in the philosophy of neuroscience, was studied. Results: An inter-level equation links the ordered sequence of interactions (organized component activities, OCAs) at system level n-1 to system behaviour (SB), the predictable behaviour of the 'mechanism as a whole' (MaW) at level n. Multiple OCAs contribute to the generation of SB, each necessary but by itself not sufficient. Jointly they result in SB by the over-summative causation of mechanisms (here called 'm-causation'). It has an interaction-time requirement given by a sum of inverse transition-rate constants. Therefore, contrary to the literature, SB is *not constituted* of its OCAs (constitution would not require time), but caused by them in an over-summative way. The m-causation supports *bottom-up* OCA → SB manipulations but, being causal, bars reverse (*top-down*) SB → OCA manipulations. *Top-down* effects are possible, but not by reversal of *bottom-up* causation.

**Key words:** Inter-level equation, master-equation, *bottom-up* causation, m-causation, *top-down* manipulation, systems neurobiology.
**Introduction**

Mayor works in the philosophy of neuroscience stress the importance of mechanisms\(^1\) in neuronal systems and arrive at novel conclusions regarding their manipulability [e.g. 1, 2]. A formal analysis of such mechanisms is attempted here. Its focus is on the way how the 'system behaviour' (SB)\(^2\), the predictable effect caused by a mechanism, is generated from component activities by over-summative means.\(^3\)

My strategy is to consider a rather general finite state model of physical mechanisms. It should apply to the probabilistic and deterministic mechanisms of neuroscience and engineering. Using a conventional formalism for the analysis of physical systems, the algebra of the general model is worked out, attempting to find an equation which links two levels of a hierarchical set of system levels. Such an equation may reveal, how the organized activity of individual components at level n-1 results in the system behaviour allocated above to level n. SB is attributed to the 'mechanism as a whole' (MaW)\(^4\) at level n.

It turned out that the formal description of mechanisms in the steady state already supplies the desired equation. With its help the controversial questions of causal versus constitutive linkage of system levels and of *bottom-up*\(^5\) versus *top-down* manipulations can be answered.

**Mechanisms**

A physical mechanism operates on its environment and changes it in a characteristic and predictable way.\(^6\) The device may have evolved or may have been constructed. Examples are an ion channel, a drug receptor, a flip-flop, a synapse. Being constituted of components in interdependent relations, a mechanism performs as an open system. Interactions of components with each other and with the environment, causal events organized in time and space, jointly result in a distinct and often reproducible system behaviour SB (or several of these). SB is driven by an environmental energy source X as specified by a level n input/output-function

\[
\text{SB} \leftarrow (\text{mechanism}^*) \times X.
\]

As will be shown, mechanism* contains an ordered sequence of time-consuming interactions (resulting in state transitions) which justifies the asymmetry-arrow in the SB(X) relation.

The following models for mechanism* may be distinguished:

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\(^1\) The term "mechanism" is commonly used with two meanings: 1. to denote the way how one thing influences another (as in "reaction mechanism"), and 2. to denote a physical device which supports this influence (as in "mechanism of a clock"). We shall use the term in its 2. sense:

\(^2\) 'Behaviour' is taken to mean a distinct sequence of events. It may be a change in environmental quantities, caused by a mechanism and attributed to its whole.

\(^3\) 'Over-summative' means a behaviour which results from an interdependence of component activities. Bertalanffy termed it 'non-summative' and 'non-trivial' [3: 67f]. Here 'over-summative' is preferred, in order to relate to the part / whole intuition of Aristotle: "The whole is something apart from the parts. It is more than their mere sum." [e.g. 4], commonly referred to as the 'over-sum principle'.

\(^4\) The term 'mechanism as a whole' was coined by W. Bechtel and C. F. Craver [1, 2].

\(^5\) *Bottom-up* is directed from the system level of components of a mechanism to the level above, occupied by the MaW.

\(^6\) Predictable in the sense of reliably occurring, but also in the sense of at least qualitatively foreseeable from the relations of the components.
**Probabilistic models:** In realistic finite-state models of molecular mechanisms state transitions are probabilistic as a fluctuating thermal energy randomly exceeds a threshold value. Yet the resulting sequence of transitions remains partially ordered as long as only one of 2 or 3 neighbouring states may participate in a change. Due to the random process repeated runs with identical initial conditions yield results differing quantitatively. However, the system behaviour SB remains qualitatively predictable, even though not quantitatively the same. For instance, while an ion channel may pass potassium ions out of a cell with a fluctuating, in detail unpredictable rate, it will nevertheless always pass potassium ions out of the cell. Such a probabilistic model is qualitatively deterministic since SB is part of the model specifications. If SB is not realized, the model was exchanged.

**Deterministic models:** Macroscopic mechanisms are usually thought to be deterministic: their design knows of only one transition to terminate a state, resulting in an ordered sequence of interactions. Molecular mechanisms can be deterministic, too. The often large number of molecular units and their large frequency of fluctuations allows the formulation of deterministic process equations based on means. These describe models of molecular mechanisms [e.g. 5, 6-8] in the deterministic limit of a population of probabilistic units, resulting in a quantitatively predictable SB. Such reproducibility is expected from empirical studies of natural and technical, molecular and macroscopic mechanisms for a large range of parameter values.

**Causal models:** Despite philosophical doubts about the reality of causation [e.g. 9, 10: 2], cause-effect relations are taken for granted in every-day situations and often also for neuronal mechanisms. For instance, W. Bechtel and C.F. Craver emphasize that within a neuronal mechanism the components interact causally [1, 2, 11]. Following J. Woodward and others, we shall adopt physical causation as a useful concept of modelling [e.g. 12: 67].

Given the correlated physical events \(e_1\) and \(e_2\), with \(e_1\) preceding \(e_2\), the following scheme of interventions will pragmatically test for causation: The path \(e_1\) to \(e_2\) may be isolated from its environment or the environment monitored for changes. A deliberate change in \(e_1\) is effected. This may result in an associated but (due to interaction) delayed change in \(e_2\). The change in \(e_2\) may occur with a certain probability only (probabilistic molecular models), or always (deterministic molecular models and macroscopic models). If the change in \(e_2\) is not explained by associated events in the environment, and if energy is exchanged in the transition \(e_1 \rightarrow e_2\), then we form the working hypothesis that \(e_1\) is the direct cause of \(e_2\) or is connected to \(e_2\) by intermediate events forming a chain of direct causes. Notably, while a deliberate change in \(e_2\) may result in an associated change in \(e_1\), this must be mediated by a linkage different from the one discussed above. For if testing shows that \(e_1\) is the direct cause of \(e_2\), than \(e_2\) is not the direct cause of \(e_1\) by inversion of pathway 1 \(\rightarrow\) 2 (manipulatory asymmetry).

In mechanisms the activity of a component corresponds to \(e_1\) and the activity of another component and ultimately of SB to \(e_2\). Additional pathways through the environment are excluded by design. This makes deterministic models of mechanisms pass the causation test. Further, since the transition \(e_1 \rightarrow e_2\) may occur with a probability \(< 1\), even probabilistic models pass...
the test. Thus all models of mechanisms are causal models. This point will be taken up when discussing equation 4.

Steady state production of SB requires that the mechanism operates in a cycle in order to recover its states [e.g. 6: 5]. The cycle organises interactions of components as an ordered sequence or, in probabilistic models, a partially ordered sequence. Figure 1A depicts such a mechanism as a device with one multi-state cycle in its state-transition diagram, describing a steady state generation of SB.

Of course, to operate in the steady state (at a distance from equilibrium) the cycle needs coupling to an energy source X supplied by the environment [13:34]. In addition the environment can supply low-energy signals. For instance, the cycle may contain one or more stable states which are terminated on receiving appropriate triggering signals from the environment. Such is the case when modelling a flip-flop.

As its name suggests, SB is attributed not to individual components but to a larger unit, the 'system' or 'whole' [3]. The whole or MaW is located on the system level above that of components. Here MaW acts on the environment, causing a change ΔEB in the environmental behaviour EB. During interaction of the MaW with the environment, the mechanism cyclically changes and recovers its states. While intrinsic properties of mechanisms remain unchanged by these interactions, extrinsic properties may be altered by feedback via EB (see below and Figure 3). In constructed mechanisms, ΔEB is the construction goal (or one of the construction goals), in evolved mechanisms it is the 'phenomenon to be explained'.

A general model

When constructing a model of finite state physical mechanisms, our aim is to obtain an inter-level equation which shows how the system level of components is in principle linked to the level of the mechanism as a whole.

The following rules and restrictions apply:

- The mechanism, engineered or evolved, is constituted of physical components subject to physical laws. Component size may be molecular or macroscopic.
- The model of the mechanism has a finite number of discrete states connected by transitions. The number of states may be small, as in modelling a flip-flop, or large, to approximate continuous variables, as in modelling a transistor.
- The transitions occur in an ordered or at least partially ordered sequence.
- The transition-state diagram of the mechanism contains at least one cycle of states.
- Any mechanism operates on its environment and changes it in a characteristic, at least qualitatively predictable way. The environment may have feedback effects on the mechanism.

The steps of derivation are:

1. We list the model states (finite number), the components of the model and their properties (transition-rate constants). Transitions will be understood as 'organized component activity'

11 Intrinsic properties of components (e.g. some first-order rate constants) are not affected by the environment. Hybrid properties of components (some first- and second-order rate constants) are co-determined by intrinsic and extrinsic (i.e. environmental) quantities. Extrinsic quantities are those which remain when the mechanism is removed.
2. Based on the lists, we draw the state-transition diagram, a graphic version of the master equation (Figure 1A). In the transition $S_1 \rightarrow S_2$, mediated by the rate constant $k_{12}$, application of a force associated with $S_1$ is the direct cause of a motion leading to $S_2$. In $S_1 \leftarrow S_2$ mediated $k_{21}$, a force associated with $S_2$ is the direct cause of a motion leading to $S_1$. Thus the two anti-parallel arrows stand for distinctly different causal pathways. The diagram contains at least one cycle of states, to make the model capable of steady-state system behaviour $SB$ [e.g. 6: 5]. The presence of several multi-state cycles results in one $SB$ for each.

3. Based on the state-transition diagram we formulate the master equation, a set of first-order, linear differential equations. It is an empirical relationship in which state-occupation probabilities $P$ (rather than forces driving the OCA's) are the variables:

$$\dot{P} = A \cdot P,$$

where $A = [k_{i,j}]$ is a square matrix of transitions of order $m \times m$ while $\dot{P} = [dP_i/dt]$ and $P = \{P_i\}$ are column vectors of order $m$. The coefficient matrix $A$ specifies the interdependence of all probabilities by the rate of transitions of states. Rate constants are time independent. Their numerical choice is subject to the constrain of microscopic reversibility: in the absence of an extrinsic force $X$ acting on a cycle of states, the product of forward rate constants should equal the product of reverse rate constants (Wegscheider condition for zero net flow). At equilibrium there is detailed balance: for each pair of adjacent states the forward rate equals the reverse rate.

4. We normalize with the conservation relationship $P_0 + P_1 + ... = 1$. For $dP_i/dt \neq 0$ the time course of transitions is a fluctuating steady state which may be exemplified with a Monte Carlo procedure. Due to random decisions the result will be probabilistic, two runs starting with the same initial conditions yielding differing results.

5. We assume a steady state by setting the $dP_i/dt$ to zero. For models of molecular mechanisms the condition $dP_i/dt = 0$ is justified for large ensembles of $N$ independent molecules in parallel (ensemble averaging [e.g. 6: 225]). With $N_i = N \cdot P_i$ and $\sum N_i = N$, mean values of $N_i$ and fluctuation term $\Delta N_i$ are related to $N_i$ by

$$N_i = \bar{N}_i + \Delta N_i$$

The mean $\bar{N}_i$ increases proportional to $N$ but the fluctuation term $\Delta N_i$ only with $\sqrt{N}$. This relative decrease justifies a neglect of $\Delta N_i$ for large $N$. We obtain with $m' = m-1$

$$\begin{bmatrix} 0 \\ 0 \\ N \end{bmatrix} = N \cdot B \cdot P = \begin{bmatrix} -k_{00} & k_{10} & \ldots & k_{m'0} \\ k_{01} & -k_{11} & \ldots & k_{m'1} \\ \ldots & \ldots & \ldots & \ldots \\ 1 & 1 & \ldots & 1 \end{bmatrix} \cdot \begin{bmatrix} \bar{P}_0 \\ \bar{P}_1 \\ \ldots \\ \bar{P}_{m'} \end{bmatrix}$$

6. For anyone cycle of states we select a pair of transition steps (from state $i$ to $i+1$ and from $i+1$ to
i) whose difference defines the mean steady state system behaviour SB associated with the cycle:

\[ SB_N = N \cdot (k_{i+1,i} P_{i+1} - k_{i,i+1} P_i) \]

(3)

where \( N \) is the number of independent units in the ensemble.

7. We eliminate the ensemble mean probabilities with Cramer’s rule, setting e.g. \( P_i \) equal to the ratio of determinants \( \frac{|B_{i+1}|}{|B|} \):

\[ SB_N = \frac{N \cdot (k_{i+1,i} |B_{i+1}| - k_{i,i+1} |B_i|)}{|B|} \]

(4)

Thus we obtain for one multi-state cycle of the state-transition diagram the ensemble-mean system behaviour in terms of net cycle turnover. The appearance of \( |B| \) on the right-hand side means that all transitions are necessary for the generation of SB. Incidentally, the quotients \( \frac{|B_{i+1}|}{|B|} \) and \( \frac{|B_i|}{|B|} \) make equation 4 non-linear with respect to rate constants (even though the master equation is linear).

Alternatively, we may use the King-Altman approach [14] which was preferred by T.L. Hill [6], where SB is calculated from the difference of the turnover rates of forward and reverse cycles (Figure 2B). This in part graphical procedure, based on mean probabilities, also requires that averaging yields only negligible noise terms. Here, too, the condition \( \frac{dP_i}{dt} = 0 \) holds for mean \( P_i \) in large ensembles.

Of course, for single molecules the time course of transitions is always probabilistic, even when the molecule is part of an ensemble in the steady state. Random transitions, computed with a Monte Carlo procedure, are shown in Figure 2C.

Be it by one of the algebraic matrix methods or by the King-Altman approach, we obtain a mean system behaviour as net cycle turnover. It is solely determined by transitions, elements of \( [B] \). State-occupation probabilities exist as means, of course, but were eliminated in the equation. Thus equation 4 describes a mean system behaviour SB in terms of all transitions (OCAs) of the model, and only of these. At large \( N \) the same parameter values deterministically yield identical results, at small \( N \) they yield at least qualitatively the same results. In any case the pragmatic test for causation (see above, "Causal models") would show that the OCAs jointly are the direct cause of SB.

8. We note how the \( SB_N (= SB_1 N) \) is converted into \( \Delta EB \), a change of environmental (extrinsic) quantities. These, in turn, may feedback onto OCAs (Figure 3). For instance, a second-order rate constant, which contains a concentration factor as an extrinsic parameter, may be part of the mechanism. If SB changes this concentration, the environmental feedback loop is complete. In systems view EB links to OCAs by an identity of concentration on level \( n \) and \( n-1 \). Feedback can be abolished by clamping the concentration to a constant value. Components (but not OCAs) remain unchanged by the feedback.

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12 To be member of an ensemble in the steady state does not affect ensemble units if these are independent from each other. Dependence results for instance from environmental variables common to all units, by feedback via EB.
**Causation and the time arrow**

A flow-force relationship like \( J = g X \), where \( J \) is a flow and conductance \( g \) an idealized material constant, is linear and symmetric. It can alternatively be written to solve for \( g \) or \( X \), i.e. \( g = J/X \), \( X = J/g \). An identification of cause and effect is not attempted. However, in more realistic models conduction becomes a characteristic sequence of transitions which is ordered in time. Thereby the flow-force relation becomes an unidirectional function which, depending on the model, may be non-linear:

\[
J \leftarrow (g^*) X \tag{4a}
\]

When viewed from system level \( n \), \((g^*)\) is a black box of which only input and output need to be known. When viewed from level \( n-1 \), \( g^* \) is due to an assembly of interacting components.

The function is deterministic, it cannot be changed algebraically without changing the underpinning model [15: 408, 420]. Being unidirectional, the function is now open to a causal interpretation based on the Newtonian concept that forces are causes and motions (flows) their effects while transfer of energy is their linkage, a requirement for interaction. Thus the extrinsic force \( X \) on level \( n \) causes the flow \( J \) by means of the conduction-mechanism \( g^* \) specified on level \( n-1 \). Of course the pragmatic test for causation (see "Causal models") has to be met on each level.

Note that the arrow indicates the direction of time in an ordered sequence of time-consuming transitions specified in the \( g^* \)-model. Thus overall reversibility is not given. This corresponds to the manipulatory asymmetry of causal relations [e.g. 16: 36]. While \( J \) may feed back onto \( X \) using pathways not specified here, it cannot do so by back-tracing the i/o-function.

Relationship 4, too, is an i/o-function, with transitions \(^{13}\) causing other transitions and ultimately SB. The time of interaction required for the generation of SB (see below) clearly excludes the alternative, a constitutive relation. A change in SB, which is net cycle turnover, can be effected by deliberately changing transition rates. Notably, SB cannot be changed in any other way [e.g. 17: 297]. The manipulatory asymmetry of causal relations is emphasized by replacing the equality sign in equation 4 by the time-arrow of i/o-functions:

\[
SB_N \leftarrow N \cdot (k_{i+1,j} |B_{i+1}| - k_{i, j+1} |B_j|) / |B| \tag{4b}
\]

In equation 4b the extrinsic energy or 'force' \( X \) is not explicit, but can be calculated. For a cycle of states \( X \) is given by the extended Wegscheider relationship

\[
X = RT \ln \left( \frac{k_{1,0} \cdots k_{2,1} \cdots k_{3,2} \cdots \cdots k_{0,m'}}{k_{0,1} \cdots k_{1,2} \cdots k_{2,3} \cdots \cdots k_{m',0}} \right) \tag{5}
\]

where \( R \) is the gas constant and \( T \) the absolute temperature. The numerator describes the forward cycle and the denominator the reverse cycle. Without energy supplied by the environment (\( X = 0 \)) the rates of forward and reverse cycle are equal, the steady state gives way to equilibrium [13:34].

The i/o-function \( SB_N \leftarrow (\text{mechanism}^*) X \) can be visualized by varying one rate constant and computing for each of its values the driving force \( X \) with equation 5 and the system behaviour SB

\(^{13}\) more strictly the forces behind the transitions or OCAs
with equation 4. The function is generally curved even though the master equation is linear.

**m-causation**

Equation 4 tells us that the SB is dependent on *all* transitions in the combination given by the right hand side expression, and only on these. Each transition contributes as necessary but not sufficient for the result, a special case of a contributory cause. Thus SB is the over-summative effect caused *exclusively* by the working assembly of components and attributed not to individual components but to the MaW. This special kind of causation, related to contributory causation, will be termed 'm-causation'. It is characteristic for finite state mechanisms generally, as these necessarily have multiple transitions and at least one SB generated by a cycle of states.

One may choose not to adopt the system view, i.e. not to embed the mechanism in a hierarchical system of levels. However, if one adopts the system view, then the (for large N deterministic) equation 4 is *inter-level* because the MaW which shows the SB is located one system level above that of components showing the OCAs. Then the m-causation discussed here, an over-summative causal and (therefore) unidirectional step, is a *bottom-up* step (Figure 3).

**Time requirement**

The mean time of interaction spent in anyone state is given by inverse rate constants [e.g. 6: 225]. If the transition is state $i+1 \rightarrow$ state i, the mean dwell time in state $i+1$ is given by $1 / k_{i+1, i}$. To complete a cycle (and thus generate SB) more time is required. By addition we obtain the lower limit of the ensemble-mean time needed to complete a cycle in the forward direction:

$$t_{cycle} \geq \sum_{i=0}^{m'} \left( 1 / k_{i+1, i} \right)$$

(with index $m'+1 = index 0$). This time requirement would become obvious in level n testing: A deliberate change in EB will cause a delayed change in SB (Figure 3). Equation 5 clearly excludes a non-causal, constitutive *bottom-up* relationship as origin of SB. For constitutive relations, which are not interactive, have no time requirement but are synchronic. The alternative is a causal (m-causal) relationship.

**Probabilistic vs. deterministic**

In the probabilistic models considered a state can be terminated by one of two or three possible transitions, which are selected randomly. Thus the sequence of interactions remains partially ordered. Such models show a fluctuating SB which is not quantitatively identical in repeated runs. However, the qualitative nature of SB remains unchanged. Further, the dependence of SB on all components and a time requirement for its production applies, as it does in the deterministic limit.

Models of finite-state macroscopic mechanisms are typically deterministic: the design ascertains that any state can be terminated by only one possible transition. There is an ordered sequence of interactions, the state-transition diagram is (in the single cycle case) given by one of the diagrams of

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14 In principle, a contributory cause may be neither necessary nor sufficient. Our cause is necessary but not sufficient.

15 e.g. C.F. Craver states: "...the constitution relationship is synchronic" [2: 153]. See also P. Ylikoski: "Causation deals with processes and events, whereas constitution deals with properties and objects. Causal processes take time, but the relations of constitution are synchronic." [18].
Figure 2B. System behaviour, described by equation 4, is quantitatively predictable. The dependence of SB on all components and a time requirement for its production are true for macroscopic mechanisms.

**Manipulability**

System level n-1 containing components, with their behaviour OCA, is linked to level n containing the MaW, with its behaviour SB, by an m-causal relationship. Being causal, the linkage is unidirectional, bottom-up only. Therefore the OCA → SB link considered has bottom-up but not its inverse, top-down manipulability. As shown in Figure 3, down-manipulation is possible by utilizing the feedback branch originating in EB, not by back-tracing the bottom-up link, which is m-causal.

In contrast, W. Bechtel and C. F. Craver suggest that the linkage of system levels is not causal but constitutive and that top-down manipulations are possible by inversion of the constitutive link. Without proving their points formally, linkage is taken to be directionally symmetrical [1, 2: 195, 11: 153]. However, their constitutive relationship is a parts/whole relation which is not symmetrical [19, 20]; see also [18, 21].

**Reductive explanation**

of mechanisms is possible because the cause for the system behaviour of a 'mechanism as a whole' is, in fact, modelled as interaction of its components at the level below. The empirical laws (or strong regularities) governing the SB root in those of a lower level and are explained by them.

However, reduction is not deduction: We cannot deduce the laws at level n-1 from those at level n. This is not possible because detail is lost when proceeding upward from n-1 to n. Rather, the laws at level n-1 are found from independent research at level n-1. Then to reduce a system behaviour at level n to level n-1 we make use of a trial-and-error bottom-up procedure. We construct a working-model at level n-1 (at the bottom) from hypothetical components and their relations, using known laws of the lower level. We note upwards the level-n-behaviour SB' of the model and compare it with the explanandum SB. In a recursive process we modify the model until its bottom-up behaviour agrees with the explanandum. We may thus find the most satisfactory model for the SB-data at hand. Then we have reduced SB, explaining it with a mechanism at the next lower level.

Since components are themselves composite objects (wholes), there is a downward cascade of components. When following this cascade, we presumably find the ultimate- or zero-level. Laws are ultimately based on those of the zero-level, where objects are not composed of components any more and where time and space lose their meaning. This 'causal drainage' is controversially discussed in [22-24].

**Conclusion**

A mechanism (as a physical device) is an open system defined on level n by an input/output function. The black-box of this function is modelled on level n-1 by an ordered sequence of component interactions, driven by environmental energy. Jointly the interactions cause the system behaviour SB. Each of the interactions contributes in an over-summative way here called m-causation. The SB is attributed to the system-whole and affects the environment of the whole in a predictable way.
An algebraic formalism commonly employed in the analysis of physical systems, the master-equation, is utilized for modelling neuronal and other mechanisms in a general way. It allows to formally answer questions posed in neuronal systems theory.

Based on the interpretation of equation 4 as an inter-level equation, my main arguments are: (1) According to equation 4, the system behaviour SB is directly dependent on the activity of each component but must be attributed to the joint action of all components, i.e. to the whole of the mechanism. This allocates SB to the system level of the MaW, level n, it makes the m-causal generation of SB a bottom-up process. (2) Further, according to equation 5, appropriate testing would reveal that the generation of SB requires time due to interaction of components. This excludes a constitutive (synchronous) origin of SB, suggested by others, and leaves the alternative: SB must be due to bottom-up causation. Top-down effects are possible using different paths, but not by reversal of bottom-up causation.

These arguments apply to all finite state models of mechanisms, as these have multiple components and transitions and one or more cycles of states generating over-summative SBs.

Outlook
Is the deterministic nature of mechanisms compatible with unpredicted or creative behaviour? Neuronal systems organize a large number of mechanisms into networks of complex function. The wholes of these networks or modules will be allocated to system levels above n. If networks are sufficiently complex, their behaviour is difficult to predict. Even if reduction were possible in principle it may fail in praxis. Now it depends on how we interpret our failure to reduce. Is it due to a lack of analytical ability or is randomness generated from deterministic processes or is at least one process indeterministic? As long as we don't know, unpredicted 'creative' output remains compatible with deterministic SBs of the mechanisms involved, meaning that none off the three possibilities was excluded.

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Figure 1. (A) Partial state-transition diagram of a probabilistic model, here showing a single multi-state cycle (with its energy supply X). System states are mutually exclusive and, for simplicity, correspond to active components (except S0). At any time there is only 1 or no active component in this example. As shown component 2 is active, S2 is realized (red). At S0 all components are at rest. Green numbers are indices of transition-rate constants k. (B) Organized component activities (OCAs) depicted as coupled interaction events. Transition from system state 2 to 1 means that component 2 goes to rest while component 1 activates. Which of the two alternative pathways (two red arrows pointing away from Com2) will be taken, is a random decision based on the relative values of two rate constants: $k_{21}$ and $k_{23}$. If the transition is state 2 $\rightarrow$ state 1 via $k_{21}$, the mean dwell time in state 2 is given by the inverse of $k_{21}$. 
Figure 2. Probabilistic and deterministic model (not showing energy supply of cycles). A: In the probabilistic case of a single molecule, the molecule is shown in state 1 (component 1 active) and can leave this state along one of two alternative paths (2 red arrows). The choice is random, constrained by the relative values of the two rate constants. B: In the steady state of ensemble means the deterministic case applies. Here SB can be calculated from the difference of the turnover rates of forward and reverse cycles without resorting to random decisions [14]. C: Time course of transitions of a 3-state model of one molecule, obtained with a Monte Carlo procedure. Such random behaviour is expected even in the ensemble steady state.
Figure 3. Components showing a cycle of OCAs on system level n-1, and MaW showing SB on level n. The vertical bracket with bottom-up arrow stands for the over-summative, m-causal process, which requires a full cycle of states. $SB_N = SB_1$ N is the ensemble behaviour. It co-determines the environmental behaviour EB. This, in turn, may feedback onto OCAs.