

# The Mathematical Aspects of our Published Cooperative Specificity Theory: The Entropy Change, ( $\Delta S$ ), Potentiates Protein – Protein Interaction

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## Abstract

The Co-operative Specificity Theory explains the reciprocal recognition between specific MHC DR/DQ molecules in a haplotype resulting in a co-operation that precipitates susceptibility to T1D. Co-operativity between protein molecules is the probable formation of one H-bond which seduces the formation of a greater number of H-bonds leading to a strong association between the two molecules. In co-operative specificity the binding between positively and negatively charged aa residues on the specific DR- and DQ-molecules occurs in a procedure that is rapid, exact and in an all-or-none fashion resulting in only one achieved maximal extremum. We theorize that protein molecules in the proteome sense each other's level of entropy  $\Delta S$  in search of partner parity, with lowest  $\Delta S$  existing between two molecules spelling co-operativity with resulting expansion of  $\Delta S$ .

**Keywords:** Protein; Protein interaction; Cooperativity; Entropy; Mean value theorem; Epigenetic; Incomplete penetrance

**Abbreviations:** MHC: Major Histocompatibility Complex; T1D: Type 1 Diabetes

## Introduction

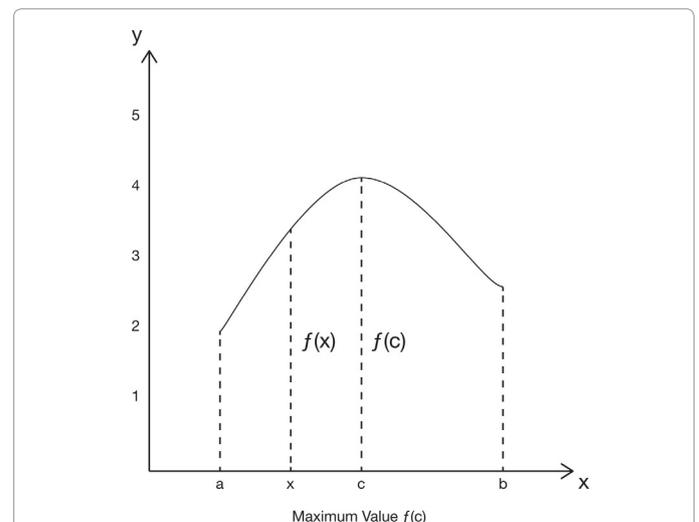
An autoimmune disease such as Type 1 diabetes (T1D) results from an aberrant immune response in which an individual's protective immune system that is normally designed to recognize and destroy invading infectious foreign bodies instead fails to distinguish self-antigens and proceeds to attack and destroy the individual's body cells, tissues and organ(s). The MHC-class II DRB1 and DQB1 genes are the prima forces which act in epistasis with some non-MHC loci to predispose the individuals to T1D [1-11]. However, there still are required environmental factors, particularly the viruses, to set in trends the calamity of autoimmunity [12-17].

The Cooperative Specificity Theory explains a phenomenon of reciprocal recognition between specific corresponding DR- and DQ- molecules in a haplotype which results in a co-operation that precipitates susceptibility to T1D in an individual. Substitution of an allele by a non-specific allele in the haplotype will abrogate the potentials of that haplotype to predispose T1D [18]. To define co-operativity we should look at the situation that proper alignments or stereospecific conformations of the protein molecules or their parts result in the probability that forming initial hydrogen-bonds is entropically favorable, resulting in protein conformational changes that enable additional bonds to form. Such enhancement of the strength of the attraction between two molecules in a protein-protein interaction by the co-operation of many weak bonds is called co-operativity [19]. This co-operativity minimises the Gibbs free energy change between the initial and final states. The weak bonds consist of H-bonds and the ionic attractions between the positive and negative charges on the protein molecules. Protein-protein interactions form the basis of the myriad intracellular functions and cellular structures [20-30]. The cooperative specificity theory narrates a special case of co-operativity.

## The Hypotheses

We suggest that the realization of our hypothesized specific co-operativity between the DR-and DQ-molecules is a very rapid and exact process and occurs in an all-or-none fashion such that we would

observe only one achieved specific extremum for a given DR/DQ pair, if we could follow this protein - protein interaction. Thus mathematically we would observe a unique maximal extremum when co-operativity is *in esse* (Figure 1), or, otherwise a minimal extremum in the absence of protein interactions (Figure 2). This situation is visible in the graph of



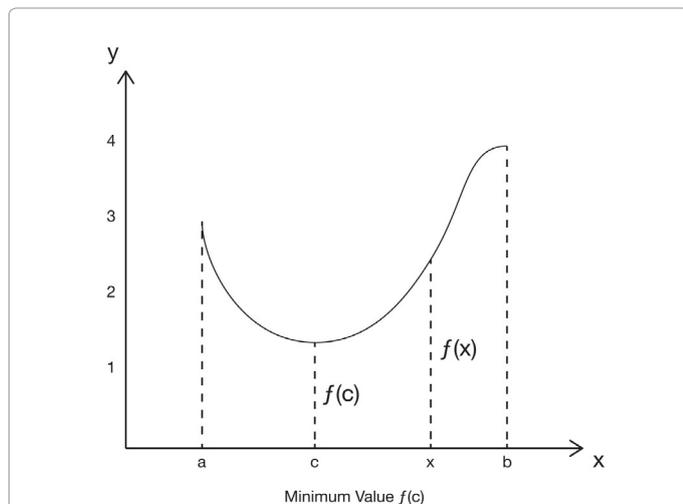
**Figure 1: Maximal Extremum.** An example of a unique mathematical maximal extremum that we would observe in the protein-protein interaction if co-operativity was in operation. In calculus, the rules of mathematical extrema state that if a function  $f$  is defined on an interval  $I$  and  $c$  is a number in  $I$ , then the function  $f(c)$  is the maximum value of  $f$  if  $f(x) \leq f(c)$  for every  $x$  in  $I$ .

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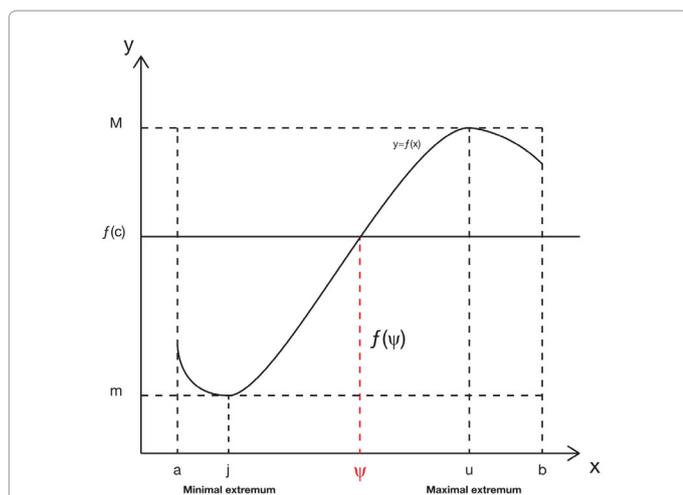
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**Figure 2: Minimal Extremum.** An example of a unique mathematical minimal extremum that would be observed in the absence of co-operativity. Similarly in calculus  $f(c)$  is the minimum value of  $f$  on  $I$  if  $f(x) \geq f(c)$  for every  $x$  in  $I$ .



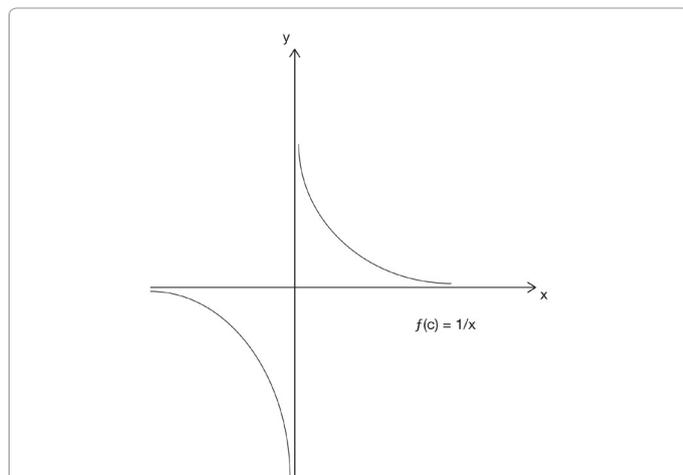
**Figure 3: The Mean Value Theorem for Definite Integrals.** Specific co-operativity between DR- and DQ-molecules is a very rapid and exact process and occurs in an all-or-none fashion such that we would observe only one-achieved specific maximal extremum for a given DR/DQ pair, if we could follow the protein-protein interaction. The Mean-Value Theorem for definite integrals summarizes this.

The Mean-Value Theorem for definite integrals where at point (mean value)  $\Psi$  the system “decides” either to progress to a maximum due to a degree of co-operativity, or to remain at minimum for the reasons already said in the above figure 3, the choice is instantaneous. The amino acid sequence specifies the three-dimensional conformation of that protein molecule, and the molecule can contain one or more recognition and highly specific non-covalent binding sites by which adjacent polypeptide subunits are bound in a specific geometrical relationship to form the characteristic complex [19]. Thus we suspect that the DR/DQ molecules achieving optimal co-operative specificity have some peculiar three-dimensional structures derived from the nature and sequences of certain amino acid residues which are evolutionarily tailored for this particular pairing and interaction. We call these amino acids the *invariant aa residues*.

The major driving force for the successful assembly of the protein pairs consists of hydrophobic interactions which are driven by the tendency of the surrounding water molecules to seek their own state of maximum entropy. Thus essentially the assembly of the molecules is entropy- driven and proceeds with a large increase in  $\Delta S$  of the aqueous surroundings. This means that as the molecules assemble themselves into a stable end-product, the free energy change,  $\Delta G$ , of the system declines to a minimal value through the maximal increase of  $(-\Delta S)$  [19].

What prompts and inertializes the molecules to interact, interact and couple specifically? We hypothesize that protein molecules in the proteome sense each other’s level of entropy for mechanistic potentials and interaction, when they are disposed for molecular cross-talks: their discovery is either co-operativity where there is low  $\Delta S$  between them, or mutual exclusivity, which is the result of, in addition to the prohibitive level of  $\Delta S$ , mutual repulsive forces that follow the preponderance and excesses of like charges, positive or negative, on (in our case) the DR/DQ molecules involved. The lowest entropy change,  $\Delta S$ , between the molecules with similar functions, facilitates approach to cooperativity, with a resulting increase in entropy change,  $\Delta S$ , in obedience to Nature’s pressure for maximal entropy- expansion in enclosed systems. Mathematically the Mean Value Theorem for definite integrals depicts the situation (Figure 3). We theorize that when co-operativity or exclusivity reaches the mean value  $\psi$ , the levels of  $\Delta S$  and  $\Delta H$  at  $dG$ , (where  $dG$  represents the infinitesimal change in free energy of Gibbs), are instantaneously equal. We rationally label  $dG$  the *isothermodynamic point*. We progress on to say that at  $dG$  the directions of  $\Delta S$  and  $\Delta H$  are parallel but opposite in sense and their magnitudes are equal. Consequentially, at the *isothermodynamic point*  $dG$ , the change in Gibb’s free energy is,  $\Delta G=0$ , following from the combination of the first and second laws of thermodynamics which says that  $\Delta G=\Delta H-T \Delta S$ . We suggest that like  $\psi$ , the *isothermodynamic point*,  $dG$ , is singular and unique for a given DR/DQ molecular pair at a constant temperature  $T$ . In fact, the emergence of  $dG$  takes place at the co-operativity,  $C=f(\psi)$ . The *isothermodynamic level*  $dG$  when  $\Delta G \leq 0$  signifies that at  $\psi$  the protein interactions “decide” to progress spontaneously to completion of co-operativity (the maximal extremum) by the increase of  $\Delta S$  (because the second law of thermodynamic states that all processes proceed in the direction which maximizes entropy (molecular randomness)). On the other hand when there is an increase in  $\Delta H$  and a decrease in  $\Delta S$ ,  $\Delta G>0$  and there will be no spontaneity in protein interactions; instead we see mutual exclusivity. We further suggest that at mutual exclusivity the protein molecules coordinate adversely to invoke a maximal  $\Delta H$  and a decrease in  $\Delta S$ .

For the reasons of precision and exactitude of concepts, we should relay or examine the existence of the co-operative specificity-axiom mathematically. In calculus, the rules of mathematical extrema state that if a function  $f$  is defined on an interval  $I$  and  $c$  is a number in  $I$ , then the function  $f(c)$  is the maximum value of  $f$  if  $f(x) \leq f(c)$  for every  $x$  in  $I$ ;  $f(c)$  is the minimum value of  $f$  on  $I$  if  $f(x) \geq f(c)$  for every  $x$  in  $I$ . The function  $f$  is considered continuous on the domain  $I$  containing  $x$ . We theorize that the function  $C$ , representing co-operativity, is a function that must have absolute extrema: either an absolute maximum at optimal co-operativity when  $C$  can be expressed as  $C=f(x) \leq f(x_0)$ , where the maximal magnitude value is  $|C|=f(x_0)$ , (Figure 1), or the absolute minimal value at mutual exclusivity when co-operativity is non-operative and  $C \geq f(x_1)$  so that  $|C|=f(x_1)$ , (Figure 2). Thus the function  $C$  cannot be represented as  $C=f(x) =1/x$  which has neither maximal nor minimal extrema, (Figure 4). We also say that the values  $|C|=f(x_0)$  or  $|C|=f(x_1)$  can take varied magnitudes, each value



**Figure 4: Absence of Extrema.** The function  $C$  cannot be represented as  $C = f(x) = 1/x$  which has neither maximal nor minimal extrema and is thus excluded in our hypothesis.

depending on the DR/DQ pair of molecules under study. The Mean-Value Theorem for definite integrals incorporates figure 1 and 2: it aptly depicts the notion of co-operativity between DR and DQ molecular pairs. This theorem states that if  $f$  is continuous on  $[a,b]$  then there exists a point  $\psi$  in  $[a,b]$  such that  $\int_a^b f(x)dx = (b-a)f(\psi)$  (Figure 3). We theorize that  $\psi$  represents the least mean value, the primordium, where the  $f(u) > \psi$  realizes completion of co-operativity whereas  $f(j) < \psi$  spells mutual exclusivity.

The uniqueness of the mean value  $\psi$  is further validated by the consideration of the Mean-Value Theorem for triple integrals. By definition, electromagnetism is the force that causes the interaction between electrically charged particles or bodies; the areas in which this happens are called electromagnetic fields. Protein molecules are electrically charged. As such, the force of interactions between the DR and DQ molecules, co-operativity  $C$ , is an electromagnetic force and qualifies as an inverse square field force (ISFF), a vector force characterized by the equation of continuity.

$$\nabla \cdot C dV = \frac{\partial M}{\partial x} + \frac{\partial N}{\partial y} + \frac{\partial P}{\partial z} = 0.$$

$$\frac{\partial x}{\partial x} \frac{\partial y}{\partial y} \frac{\partial z}{\partial z}$$

The Mean Value Theorem for triple integrals states that if a function, (in our case  $C$ ), of three variables  $(x,y,z)$  is continuous throughout a spherical region  $Q$ , then there is a point  $\Omega(u,v,w)$  in the interior of  $Q$  such that  $\iiint_Q f(x,y,z) dx dy dz = \iiint_Q f(x,y,z) dV = f(x,y,z)|_{\Omega} V$ , where  $V$  is the volume of  $Q$  and  $f(x,y,z)|_{\Omega}$  denotes  $f(u,v,w)$ . It follows that as  $C$  is a continuous vector function, then  $\iiint_Q \nabla \cdot C dV = \nabla \cdot C|_{\Omega} V$ , where

$C(x,y,z) = M(x,y,z)i + N(x,y,z)j + P(x,y,z)k$  is, as said above, an ISFF, a vector function in three dimensions. The components  $M,N,P$  have partial derivatives, and

$$\nabla = i\frac{\partial}{\partial x} + j\frac{\partial}{\partial y} + k\frac{\partial}{\partial z}$$

$$\frac{\partial x}{\partial x} \frac{\partial y}{\partial y} \frac{\partial z}{\partial z}$$

$$\text{Thus the divergence of } C \text{ is } \nabla \cdot C = \frac{\partial M}{\partial x} + \frac{\partial N}{\partial y} + \frac{\partial P}{\partial z}.$$

$$\frac{\partial x}{\partial x} \frac{\partial y}{\partial y} \frac{\partial z}{\partial z}$$

Now, Gauss' Theorem says that:  $\iint_S C \cdot n dS = \iiint_Q \nabla \cdot C dV$ , the triple integral of the divergence of  $C$  over  $Q$ , where  $n$  is the vector normal and  $S$  is the surface of the sphere. That is,  $\iint_S C \cdot n dS = \iiint_Q (\frac{\partial M}{\partial x} + \frac{\partial N}{\partial y} + \frac{\partial P}{\partial z}) dV$ .

$$\frac{\partial x}{\partial x} \frac{\partial y}{\partial y} \frac{\partial z}{\partial z}$$

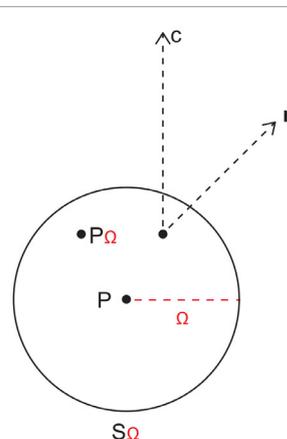
In scalar form it is written as  $\iint_S (M \cos \alpha + N \cos \beta + P \cos \gamma) dS = \iiint_Q (\frac{\partial M}{\partial x} + \frac{\partial N}{\partial y} + \frac{\partial P}{\partial z}) dV$ .

$$\frac{\partial x}{\partial x} \frac{\partial y}{\partial y} \frac{\partial z}{\partial z}$$

$$\text{It therefore follows that, from Gauss' Theorem, } \nabla \cdot C|_{\Omega} = \frac{\iint_S C \cdot n dS}{V}$$

This ratio on the right of the equation may be interpreted as the flux of  $C$  per unit volume of the sphere  $Q$ . That is the electromagnetic flux of  $C$  over  $S$  equals the triple integral of the divergence of  $C$  over  $Q$ . This immediate equation above can be shown to hold true for any point  $\Omega$  within  $Q$  and does satisfies what the Mean Value Theorems stand for (Figure 5). The point  $\Omega$  is therefore the equivalence of the point  $\psi$  cited above in the Mean Value Theorem for definite integrals. Both represent the least mean value for co-operativity and the limit of mutual exclusivity. Thus  $\psi$  or  $\Omega$  are the decisive, pivoted points at which co-operativity can or will proceed spontaneously because, in energy terms, here the *isothermodynamic* level is  $dG = \Delta G = 0$ .  $\Omega$  is the limiting value of the flux per unit volume of the sphere  $Q$ . Here the divergence is,  $\nabla \cdot C dV = 0$ , also, and it signifies the absence of sources or sinks, for the electromagnetic flux  $C$ .

We said in our second Paper (Temajo and Howard) [31] that it remains enigmatic that most people do not develop autoimmune diseases, while some do, following experience with viral infections. We now beat a retreat and back-track the trail to surmise that in the cases where no autoimmune diseases occur and yet the proper predisposing haplotypes are in place, it is because co-operativity between the specific DR/DQ molecules is probably derailed by the intervention of epigenetic modifications of the haplotypic molecules thereby abolishing, on this occasion, the power of that haplotype to predispose T1D. Indeed in hindsight the above scenario mirrors and interprets what is popularly referred to by other workers as the "incomplete penetrance" of T1D, a formulation which recognizes that some genetically primed individuals in the population do not develop the disease (Figure 6). Here in figure 6 we observe that the extremely predisposing MHC genotype DR3-DQ2/DR4-DQ8 did not mediate T1D in sibling S1 (22 years of age at the time of our TGGE analysis) but did so in siblings S2 and S3 who were both under 17 years of age. Justify! Well, identical twins are not truly identical at the molecular level as shown by some observations



**Figure 5: The Mean Value Theorem for Triple Integrals.** The flux of  $C$  per unit volume of the sphere. This signifies that the electromagnetic flux of  $C$  over  $S$  equals the triple integral of the divergence of  $C$  over  $Q$ .

that some twins differed in DNA- methylations and histone- acetylation [32]. Some examples of epigenetic modifications with consequences are listed in table 1. For the similar reasons, we are suspecting that DR-DQ haplotypes might, in detail, change with individuals or age through epigenetic modifications. Acetylation, phosphorylation, or methylation of the lysine residues on the allelic proteins, for example, would redistribute the charges on, and confer modification of the tertiary and quaternary conformations of, the protein molecules, and thereby, could install mutual repulsive forces resulting in mutual exclusivity that we hypothesized above, and efface co-operativity.

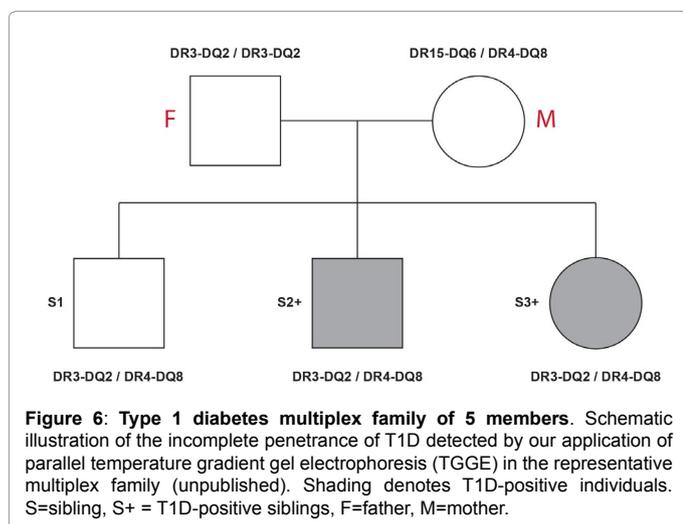
### Conclusion

In summary (Figure 7), protein–protein interactions form the foundation of intracellular functions and cellular architecture. A low level of  $\Delta S$  between a pair of molecules augurs well for their interaction. In nature there is that poised potential tendency for maximal entropy- expansion (molecular randomness) in an enclosed

system. Thus molecules that experience a low  $\Delta S$  (pertinent to the molecular pair involved) between them get mutually amorous, “in love”, and will consent, if you will, to interact co-operatively in order to expand maximal entropy. Co-operativity is a feature of protein–protein interactions where a great number of weak H-bonds act in concert to constitute a strong association between two molecules or their parts. The co-operative specificity is a particular case where only specific protein partners with appropriately commensurate low  $\Delta S$  levels will interact. In this situation co-operativity is exact and occurs in an all-or-none fashion such that we would observe only one achieved mathematical maximal extremum for a given, in our case, DR/DQ specific pair. The graph of The Mean Value Theorem for the integrals (Figure 3) incorporates the phenomena where at the mean value  $\psi$  the system “decides” to progress to a maximum, reflecting ambient co-operativity, or to remain at a minimum in the absence of protein interactions. Thus co-operative specificity between protein molecules occurs according to or within the framework of some mathematical principles. Finally, we have hypothesized that epigenetic- mediated derailment of co-operativity between DR/DQ molecular pairs begets the *incomplete penetrance* of T1D. Hither-to-fore no one has advanced or proffered an alternative explanation for the existence or underlying principle of *incomplete penetrance*.

### High-Lights

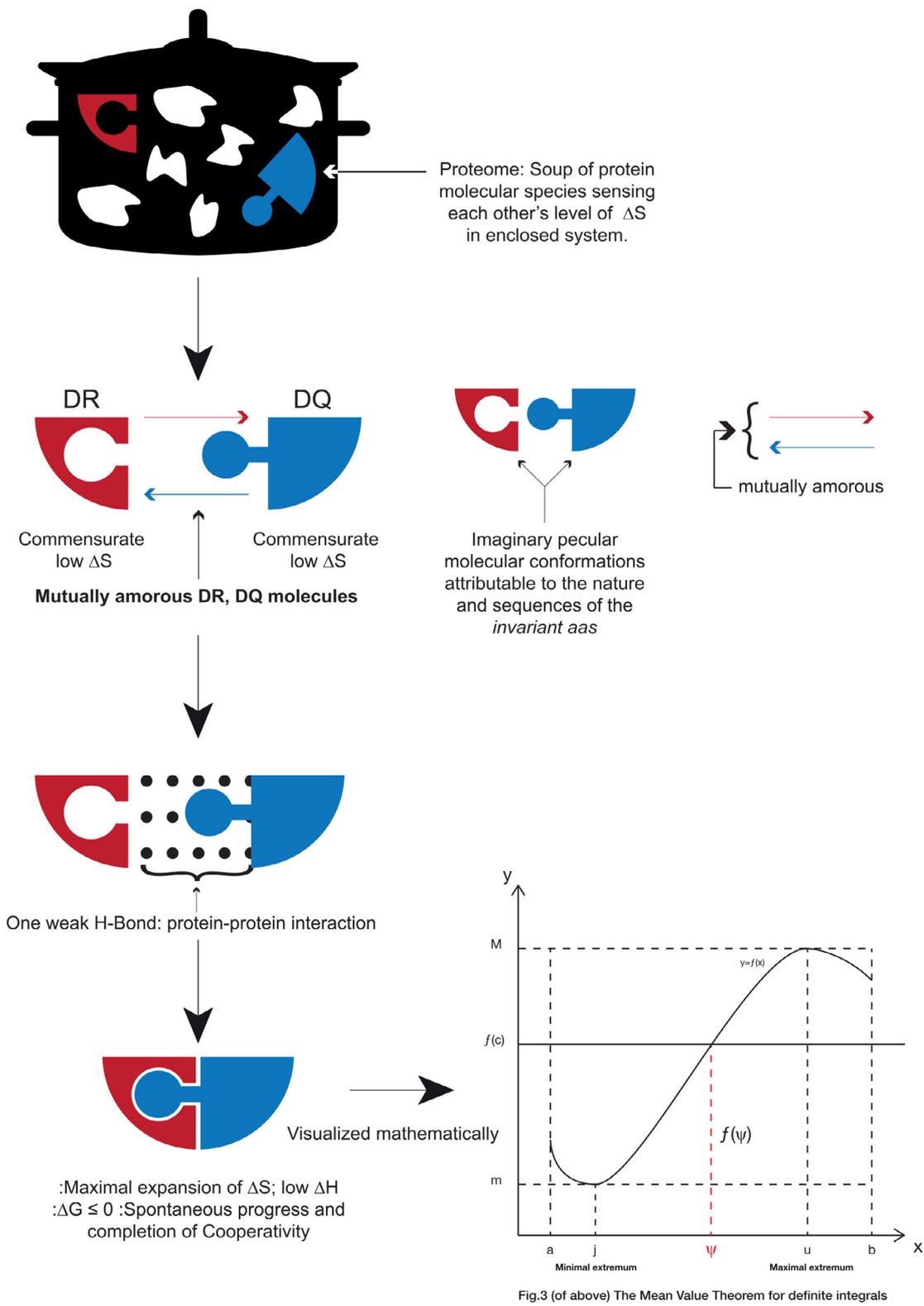
- Protein–protein interaction is fundamental in intracellular functions and cellular structures.
- Co-operativity is a feature of protein–protein interaction which results when a set of weak H-bonds coalesce and form strong bondage between a pair of interacting protein molecules.
- Co-operative specificity, as postulated, is a special case of co-operativity where protein-protein interaction demands that specific DR and DQ molecules pair in order to predispose T1D.
- The Mean Value Theorem for definite integrals mathematically depicts co-operativity and the co-operative specificity.



Histone subunit	Residue	Modification	Consequence
H2A	Serine 1	Phosphorylation	Mitosis, transcriptional repression
	Lysine 4	Acetylation	Transcriptional activation
H2B	Lysine 119	Ubiquitylation	Spermatogenesis
	Serine 14	Phosphorylation	Apoptosis
H3	Lysine 120	Ubiquitylation	Meiosis
	Lysine 4	Acetylation	Transcriptional activation
H4		Methylation	Active euchromatin
	Lysine 9	Acetylation	Transcriptional activation
		Methylation	Transcriptional repression
	Threonine 11	Phosphorylation	Mitosis
	Arginine 3	Methylation	Transcriptional activation
	Lysine 16	Acetylation	Transcriptional activation
			DNA repair
	Lysine 59	Methylation	Transcriptional silencing

Adapted from Watson et al. [32], Epigenetic modification can occur through acetylation, methylation, phosphorylation and ubiquitylation of histone subunits with different consequences to the cells through transcriptional activation or repression. The effects of such epigenetic modification of genomes may in some occasions exhibit themselves as genetic disorders. We postulate, within credence, that the above epigenetic modifications, if occurred on DR and DQ molecules, would alter the charge distributions on these molecules and consequentially derail co-operativity thereby obviating haplotypic potentials to predispose T1D: such genetically primed individuals escape this autoimmune calamity.

Table 1: Examples of epigenetic modification of molecules and their consequences.



**Figure 7: Summary: Protein-Protein Interaction.** Arbitrary protein molecular species in the proteome sensing each other's level of  $\Delta S$  for suitability and parity for interaction. It is hypothesized that certain specific DR(red)- and DQ(blue)- molecules in the proteome are mutually amorous, "in love", in terms of  $\Delta S$  and thus will couple, resulting in co-operativity with maximal expansion of  $\Delta S$ , lowering  $\Delta H$ , and promoting  $\Delta G \leq 0$ .

- At the primordial mean value  $\psi$  the decision is made whether or not a protein–protein interaction will progress spontaneously to completion of co-operativity, depending on  $\Delta G$  level. Spontaneity will happen when  $\Delta G \leq 0$ .
- In Figure 6, the extremely predisposing MHC genotype DR3-DQ2/DR4-DQ8 did not mediate T1D in sibling S1: the evidence and reality of *incomplete penetrance* are here concretized!
- Epigenetic modifications of DR/DQ molecules derail the co-operativity between them, resulting in the *incomplete penetrance* of T1D.
- Finally, in deeper thinking, we come to appreciate that Co-operative Specificity Theory [18] articulates a special situation of epistasis delineated, limited and exhibited between members of the MHC haplotypes.

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