



# 血红蛋白序列、结构和功能分析

CAAS08S1

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# 主要内容

- 一、血红蛋白及其基因家族序列分析（摘录）
- 二、血红蛋白结构及功能分析
  - 1、蛋白质结构与氧合曲线
  - 2、镰刀细胞型贫血症的蛋白质结构水平成因

# Hemoglobin

- Hemo-globin
- Hemoglobin the iron-containing oxygen-transport metalloprotein

# Types in humans

- **In the embryo:**

- Gower 1 ( $\zeta_2\varepsilon_2$ )
- Gower 2 ( $\alpha_2\varepsilon_2$ ) (PDB 1A9W)
- Hemoglobin Portland ( $\zeta_2\gamma_2$ )

- **In the fetus:**

- Hemoglobin F ( $\alpha_2\gamma_2$ ) (PDB 1FDH)

据统计至今已发现异常血红蛋白200多种,异常血红蛋白携带者有一亿多人.

hemoglobinopathy 血红蛋白病

- **In adults:**

- Hemoglobin A ( $\alpha_2\beta_2$ ) (PDB 1BZ0) 95%
- Hemoglobin A2 ( $\alpha_2\delta_2$ ) 1.5-3.5%
- Hemoglobin F ( $\alpha_2\gamma_2$ ) 有限人群
- **Variant forms** (hemoglobinopathy)
- Hemoglobin S ( $\alpha_2\beta^S_2$ ) 镰刀型细胞贫血症
- Hemoglobin C ( $\alpha_2\beta^C_2$ ) 慢性溶血性贫血

# Other oxygen-binding proteins

- **Myoglobin**:肌红蛋白。脊椎动物肌肉组织，序列及结构与血红蛋白相似，单体，储氧
- **Hemocyanin**:血蓝蛋白。自然界中第二大运氧蛋白；节肢动物与软体动物；含铜附基，氧合状态为蓝色
- **Hemerythrin**:蚯蚓血红蛋白。多种海洋无脊椎动物及少量环节动物；含铁但不具血红素；氧合粉红，无氧无色
- **Chlorocruorin**:血绿蛋白？许多环节动物；氧合红色，无氧绿色
- **Vanabins**:钒产色原？海鞘，可能以钒作蛋白附基
- **Erythrocrutorin**:无脊椎动物血红蛋白。多数环节动物，巨型蛋白复合体，分子量达350万道尔顿
- **Pinnaglobin**:平那珠蛋白。仅见于软体动物 *Pinna squamosa*。褐色含锰及卟啉
- **Leghemoglobin**:豆血红蛋白。蝶形花科植物；吸收游离氧保护根部固氮菌

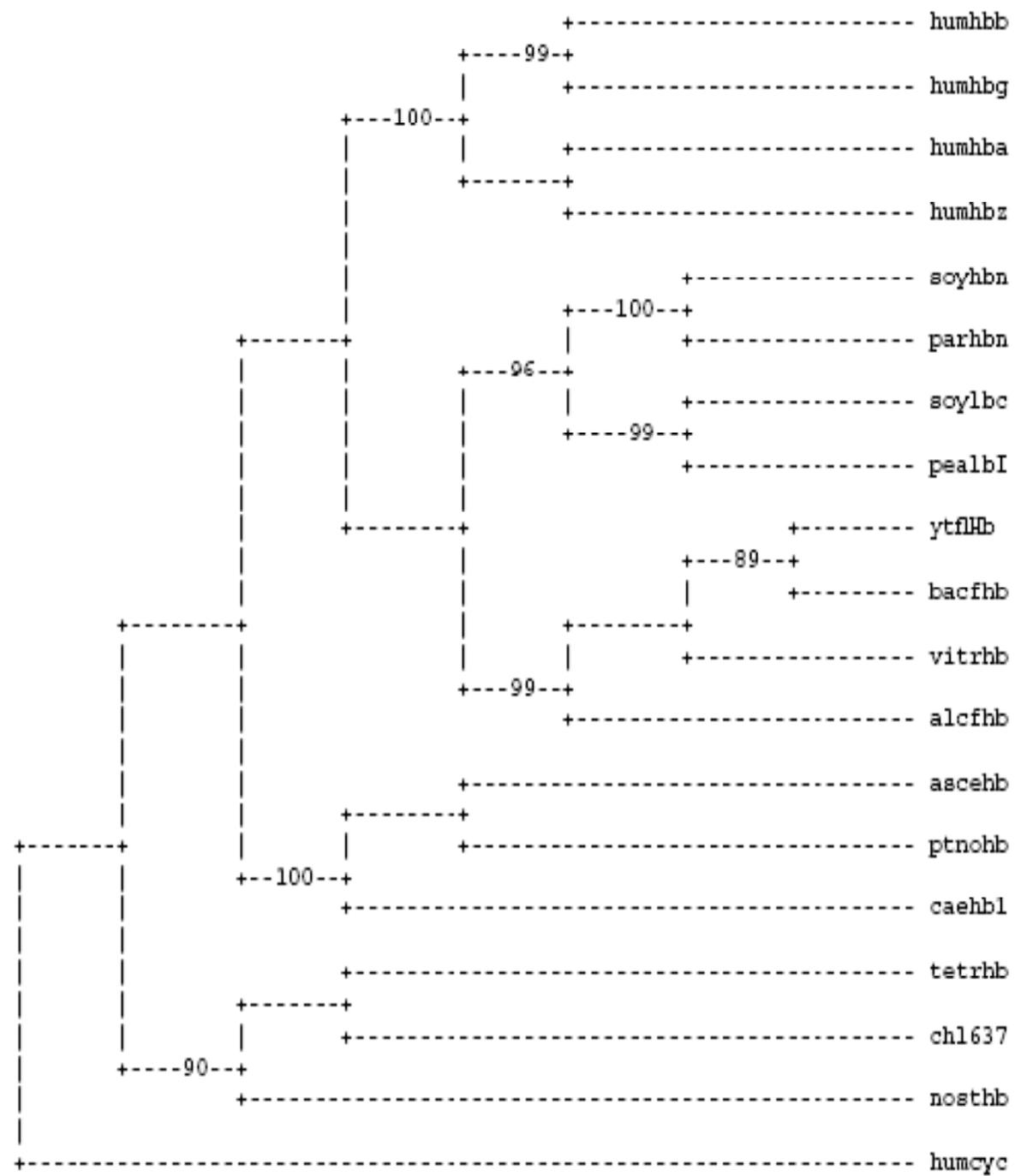
# 一、血红蛋白 及其基因家族序列分析

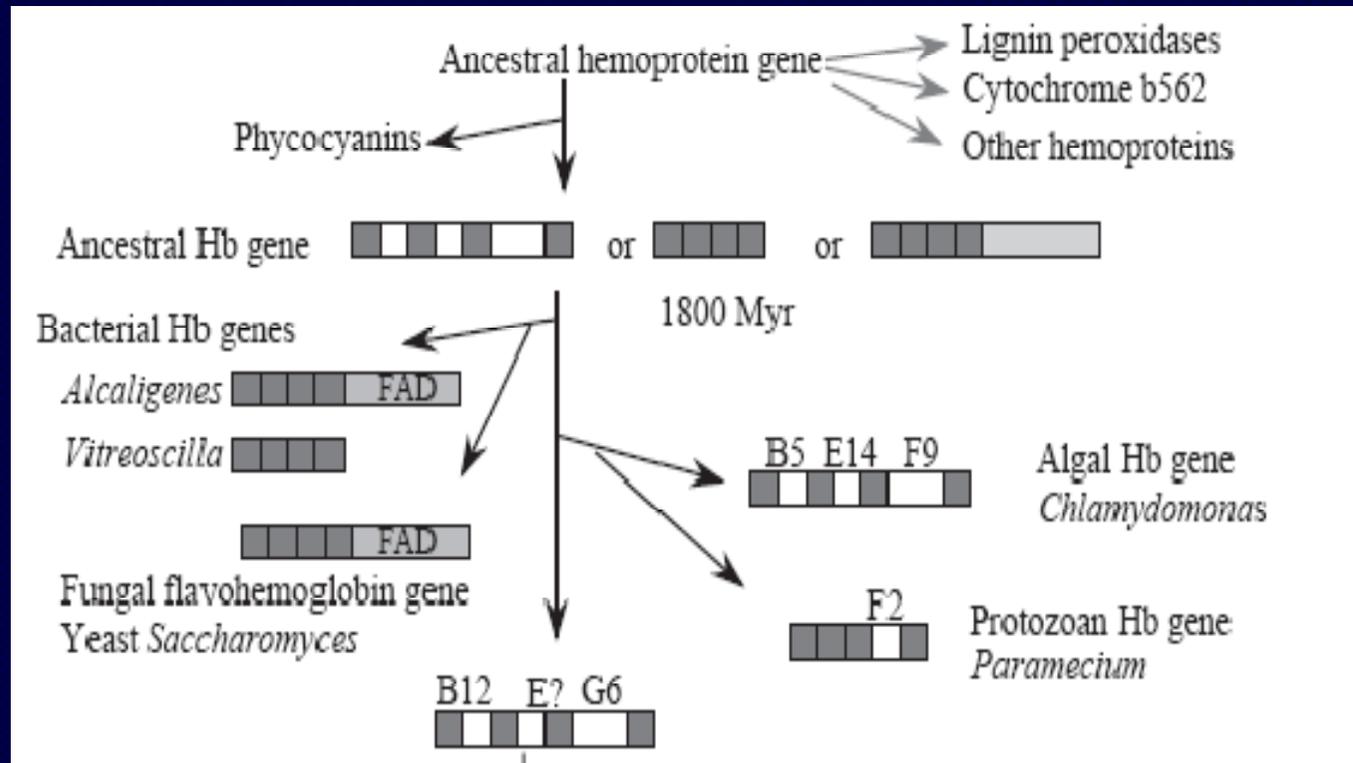
Table 1. Selected hemoglobins illustrate the diversity of proposed functions and regulation

Class	Exemplary genus	Hemoglobin	Regulation	Function (demonstrated and proposed)
Vertebrate	<i>Homo</i>	HbA	Hypoxia-induced increase in production of erythropoietin, which stimulates proliferation and differentiation of erythroid precursors, the progeny of which express Hb at a high level	Oxygen transport between tissues
Plant	<i>Glycine</i>	Lb	Nodulin-specific increase in transcription	May sequester oxygen away from nitrogenase May transport oxygen to electron transport chain in nodule
Plant	<i>Glycine</i>	Nonsymbiotic Hb	Induced by hypoxia?	Intracellular oxygen movement
Alga	<i>Chlamydomonas</i>	LI637 Hb	Light-inducible expression in chloroplast	Oxygen bound to LI637 Hb can be reduced. It may serve to accept electrons, sequester oxygen or deliver oxygen inside the organelle
Fungi	<i>Saccharomyces</i>	YHB (a flavo-hemoglobin)	Induced by high levels of oxygen or reactive oxygen species, or by blocking electron transport Repressed by hypoxia Induction is mediated by the transcription factors HAP1 and HAP2/3/4	Can transfer electrons from NADPH to heme iron May serve to protect from oxidative stress
Bacteria	<i>Alcaligenes</i>	FHP (a flavo-hemoglobin)	Induced anaerobically Promoter contains a potential binding site for NarL and FNR	Proposed electron transfer Possible role in anaerobic metabolism, perhaps gas metabolism during denitrification
Bacteria	<i>Vitreoscilla</i>	Hb	Induced by hypoxia Promoter contains binding sites for FNR	Can serve as terminal electron acceptor during respiration May scavenge oxygen

	A helix----->		B helix----->		C helix>		D helix>		E helix---		----->		
	1	15 16	30 31	31	45 46	46	60 61	61	75 76	76	76	90	
				P	F				'H'				
humhbb	-----	VHLTPEEK	SAVTALWGKVN--	VD	EVGGEALGRLLVVYP	WTQRFESFGDLSTP	DAVMGNPK----	VKA	HGKKVLGAFSDGLAH				77
humhbg	-----	GHFTEEDK	ATITSLWFKVN--	VE	DAGGETLGRLLVVYP	WTNRFDSFGNLSSA	SAIMGNPK----	VLA	HGKKVLTSLGDAIKH				77
humhba	-----	VLSPADK	TNVKAAWGKVGAG		BYGAEALERMFLSFP	TTKTYFPHF-----	DLSHGSAQ----	VKG	HGKKVADALTNAVAH				72
humhbx	-----	SLTKTER	TIIVSMWAKISTQAD		TIGTETLERLFLSHP	QTKTYFPHF-----	DLHPGSAQ----	LRA	HGSKVVAAVGDAVKS				72
soyhbn	--	TTTLERGFSEEQE	ALVVKSWNVMMKNSG		ELGLKFFLKIFEIAP	SAQKLFSFL-----	RDSTVPLEQNPCLKP		HAVSVFVMTCDSAVQ				82
parhbn	MSSSEVNKVFTEEQE		ALVVKAWAVMMKNSA		ELGLQFFLKIFEIAP	SAKNLFSYL-----	KDSPVPLEQNPCLKP		HATTVFVMTCESAVQ				84
soylbc	-----	GAFTEKQE	ALVSSSFRAFKANIP		QYSVVFYNSILEKAP	AAKDLFSFL-----	ANGVDPTN--	PKLTG	HAEKLFALVRDSAGQ				75
pealbI	-----	GFTDKQE	ALVNSSSE-FKQNL	P	GYSILFYTIVLEKAP	AAKGLFSFL-----	KDTAGVEDS-	PKLQA	HAEQVFLVRDSAAQ				74
ytflHb	-----	MLAEKTR	SIIKATVPVLEQQGT		VITRTFYKNMLTEHT	ELLNIFNRT-----	NQKVGAPQ----	N-A	LATTVLAANKNIDDL				71
bacfhb	-----	MLDNKTI	EIIKSTVPVLQQHGE		TITGRFYDRMFQDHP	ELLNIFNQT-----	NQKKKTQR----	T-A	LANAVIAAANIDQL				71
vitrhb	-----	MLDQQTI	NIIKATVPVLKEHGV		TITTFYKNLFAKHP	EVRPLFDMG-----	RQESLEQP----	K-A	LAMTVLAAAQNIENL				71
alcfhb	-----	MLTQKTK	DIVKATAPVLAEHGY		DIIKCFYQRMFEAHP	ELKNVFNMA-----	HQEQGQQQ----	Q-A	LARAVYAYAENIEDP				71
ascehb	----	SANKTREL	CM	KSLEHAKVDT	SNEAR	QDGDIDLYKHMFEY	PLRKYFKNR----	E	BYTAEDVQNDPFFAK	QGQKILLACHVLCAT			80
ptnohb	--	AIASASKTREL	CM	KSLEHAKVGT	SKEAK	QDGDIDLYKHMFEHY	AMKKYFKHR----	E	NYTPADVQKDPFFIK	QGQKILLACHVLCAT			83
caehbl	----	NRQEISDL	CV	KSLEGRMVGTEA	QNI	ENGNAFYRYFFTNFP	DLRVYFKGA----	E	KYTADDVKKSERFDK	QGQRILLACHLLANV			80
tetrhb	-----	MNKPQ	TIYEKLG	ENAM	KAAPLFFYKVLADE	RVKHF	FKNT-----		DMDHQT-----	K	QQTDFLTMLLGGPNH		63
chl637	-----	RKCPS	SLFAKLG	REAV	BAAVDKFYNKIVADP	TVSTYFSNT-----			DMKVQR-----	S	KQFAFLAYALGGASE		63
nothb	-----	MS	TYDNIG	QPAI	BQVDELHKRIATDS	LLAPI	FACT-----		DMAQR-----	N	HLVAFLGQIFEGPKQ		60
humcyc	-----	M	GDVEKGGKIFIMKCS		QCHTVEKGGKHTGP	NLHGLFGRK-----			TGQAP-----		-GYSYTAANKNKGII		59

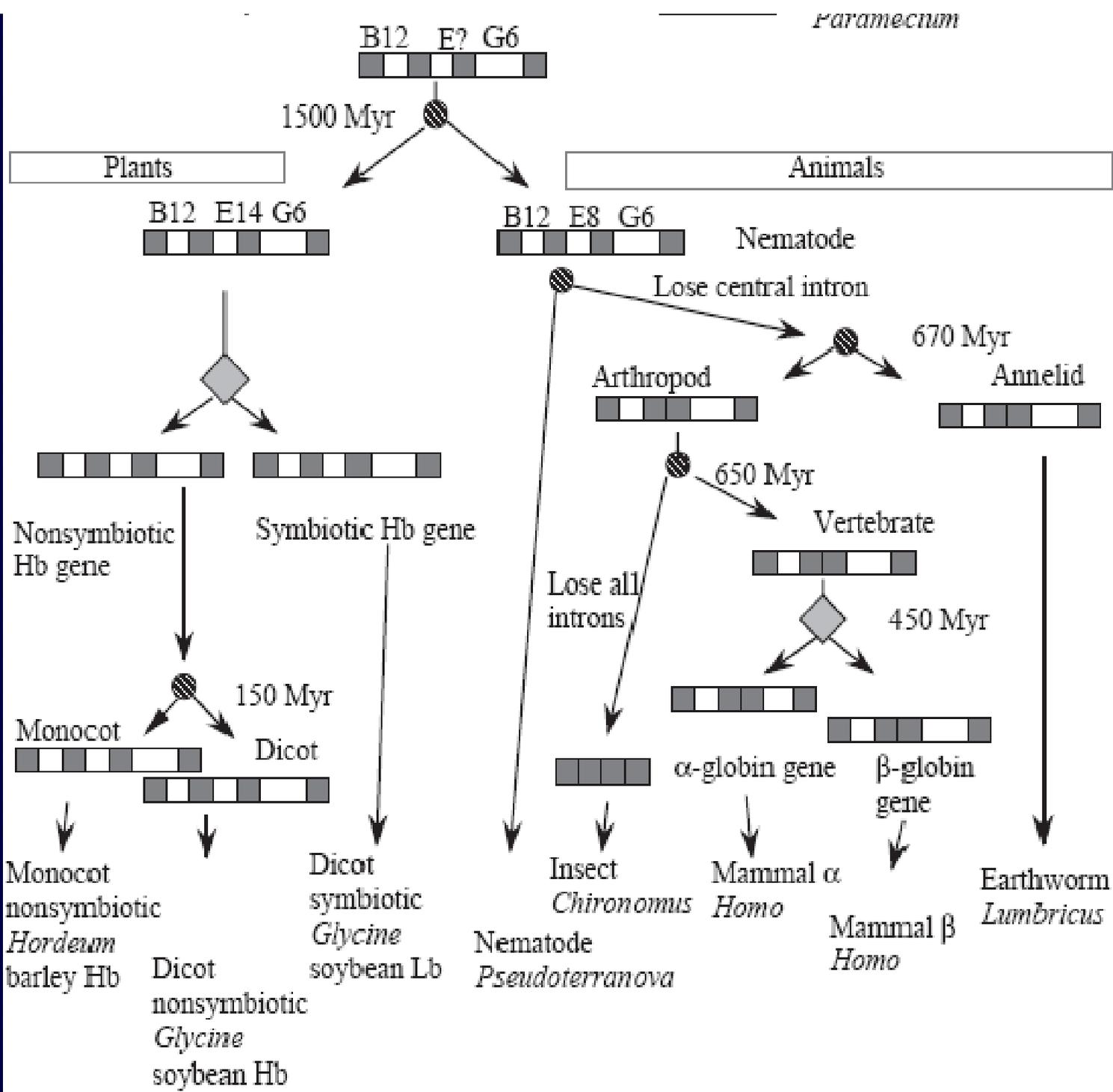
	F helix----->		G helix----->		H helix----->			
	91	105 106	120 121	121	135 136	150 151	165 166 176	
			H			'AW'		
humhbb	LDNLKGTFA-----	TLSELHCDKLHVDPE	-NFRLLGNVLCVLA		HHPGKE--FTPPVQA	AYQKVVAGVANALAH	KYH-----	146
humhbg	LDDLKGTFA-----	QLSELHCDKLHVDPE	-NFKLLGNVLTVLA		IHFGKE--FTPEVQA	SWQKMTGVSALSS	RYH-----	146
humhba	VDDMPNALS-----	ALSDLHAHKLKRVDPV	-NFKLLSHCLLVTLA		AHLPAB--FTPAVHA	SLDKFLASVSTVLTS	KYR-----	141
humhbx	IDDIGGALS-----	KLSELHAYILRVDPV	-NFKLLSHCLLVTLA		ARFPAD--FTAEAHA	AWDKFLSVSSVLTE	KYR-----	141
soyhbn	LRKAGKVTVRESNLK	KLGATHFRGTGVANE	-HFEVTKFALLETIK		EAVPEM--WSPAMKN	AWGEAYDQLVDAIKS	EMKPPSS----	160
parhbn	LRKAGKVTVKESDLK	RIGAIHFKTGVVNE	-HFEVTRFALLETIK		EAVPEM--WSPAMKN	AWGVAYDQLVAAIKF	EMKPSST----	162
soylbc	LKTNGTVVA---DA	ALVSIHAQKAVTDP	-QFVVVKEALLKTIK		BAVGGN--WSDELSS	AWEVAYDELAIAIKK	A-----	143
pealbI	LRTKGEVVLG---NA	TLGAIHVQKQVITNP	-HFVVVKEALLQTIK		KASGNN--WSEELNT	AWEVAYDGLATAIKK	AMKTA-----	147
ytflHb	SVLMDHVKQ-----	-IGHKHRALQVIKPE	-HYPIVGEYLLKAIK		EVLGDA--ATPEIIN	AWGEAYQAIADIFIT	VEKK-----	139
bacfhb	GNIIPVVKQ-----	-IGHKHRSIGIKPE	-HYPIVGEYLLKAIK		DVLGDA--ATPDIMQ	AWEKAYGVIADAFIG	IEKDM-----	140
vitrhb	PAILPAVKK-----	-IAVKHCQAGVAAA	-HYPIVGEYLLKAIK		EVLGDA--ATDDILD	AWKAYGVIADVFIQ	VEADLYAQAVE	146
alcfhb	NSLMAVLKN-----	-IANKHASLGVKPE	-QYPIVGEHLLAAIK		EVLGNA--ATDDIIS	AWAQAYGNLADVLMG	MESEL-----	140
ascehb	YDDRETFNAYTR---	ELDRHARDHVHMP	---PEVWTFWKLFE		EYLGKTTLDEPTKQ	AWHEIGREFAKEINK	HGRHA-----	153
ptnohb	YDDRETFDAYVG---	ELMARHERDHVKIP	---NDVWNHFWEHFI		EFLGSKTTLDEPTKH	AWQEIGKEPFSHEISH	HGRHS-----	156
caehbl	YTNEEVFKGYVR---	ETINRHRIYKMDPA	----LWMAFFTFTFT		GYLESVGLNDQQKA	AWMALGKEFNAESQT	HLKNS-----	151
tetrhb	YKGNMTEA-----	----HKGMNLQNL	-HPDAIENLAATLK		ELG-----VTDVIN	BAAKVIHTRKDMLG	K-----	121
chl637	WKGKDMRTA-----	----HKDLVPHLSD	VHFQAVARHLSDTLT		ELGVPP--ED-ITD	AMAVVASTRTEVLNM	PQQ-----	126
nothb	YGGRPMDKT-----	----HAGLNLQQP	-HPDAIAKHLGEAMA		VRGVS---AEDTKA	ALDRVTNMKGAILNK	-----	118
humcyc	WGEDTLMEY-----	----LENP-----	----KKYIPGTKM		IFVGIK--KK---E	BRADLIAYLKATNE	-----	105

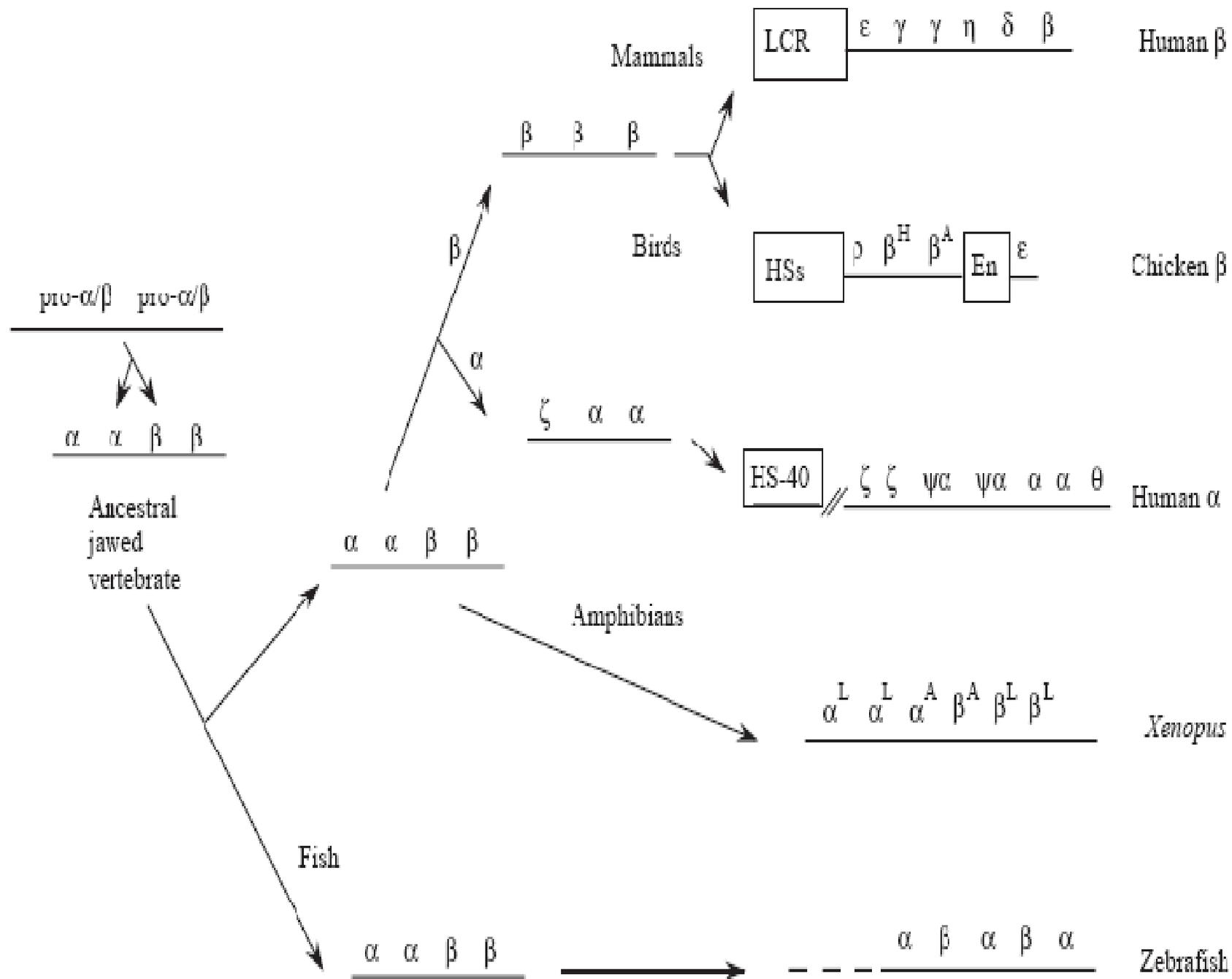




FAD: flavin-binding domain

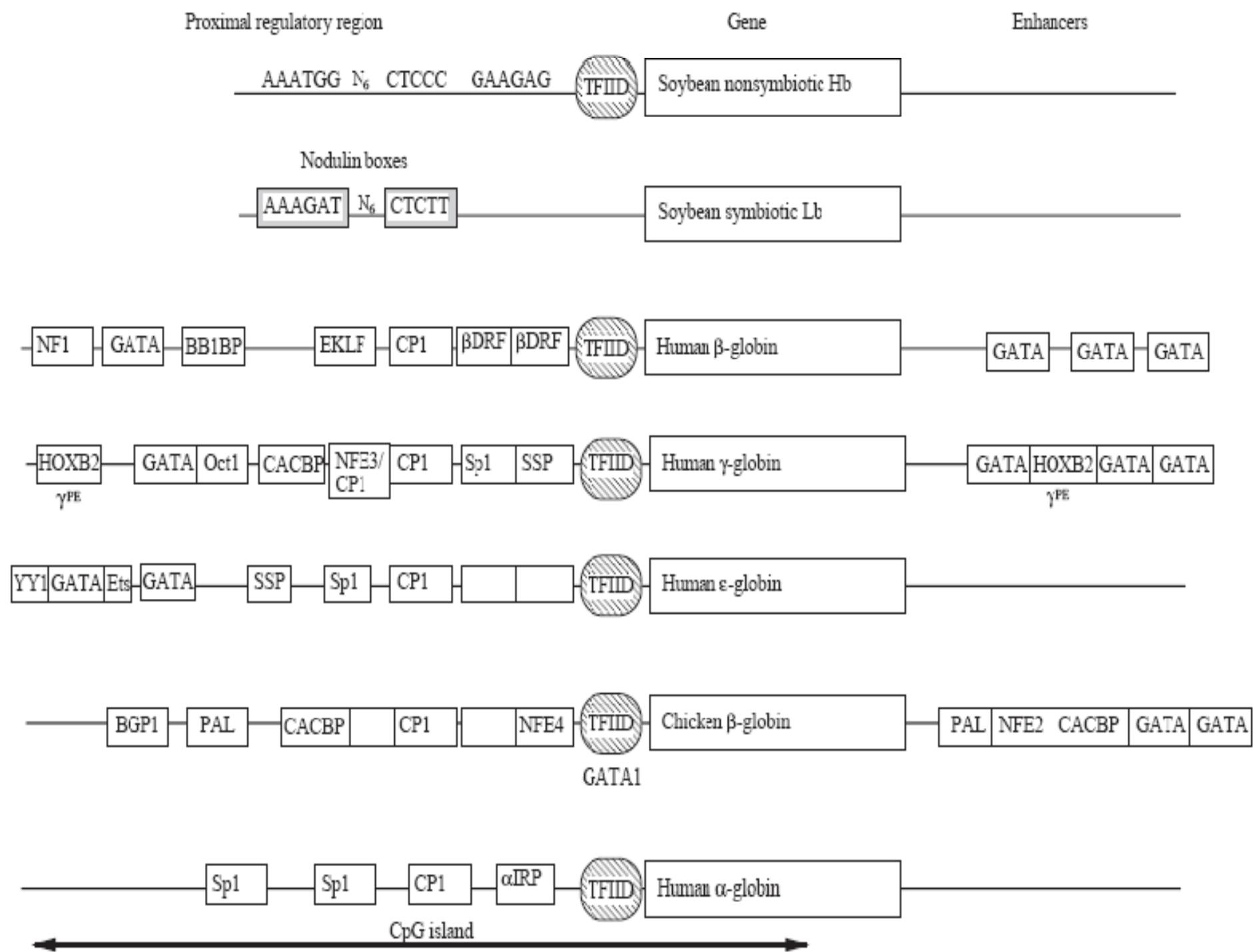
Myr: millions of years ago

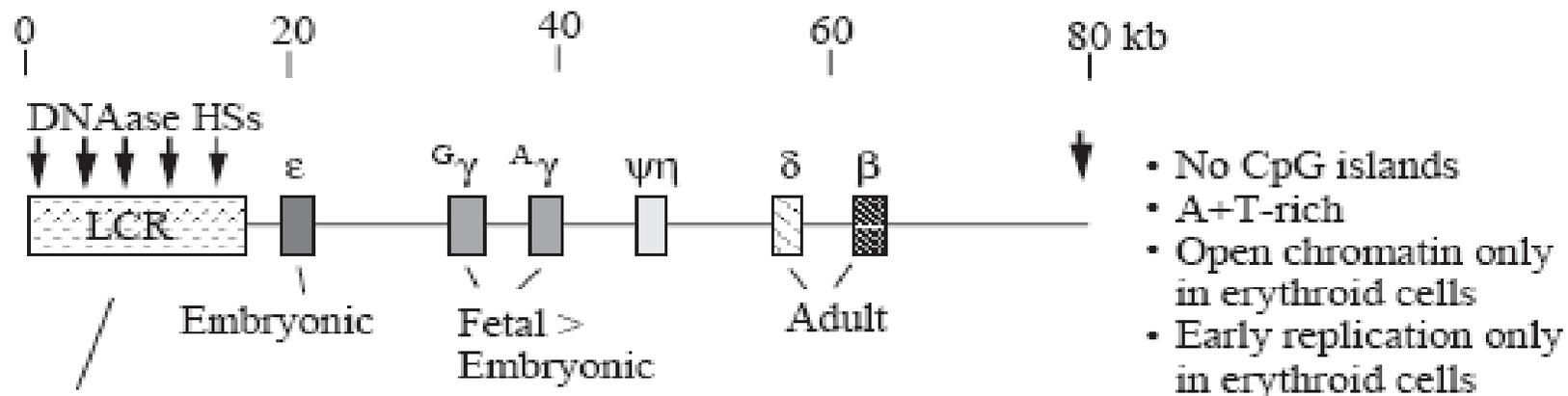




# 主要启示

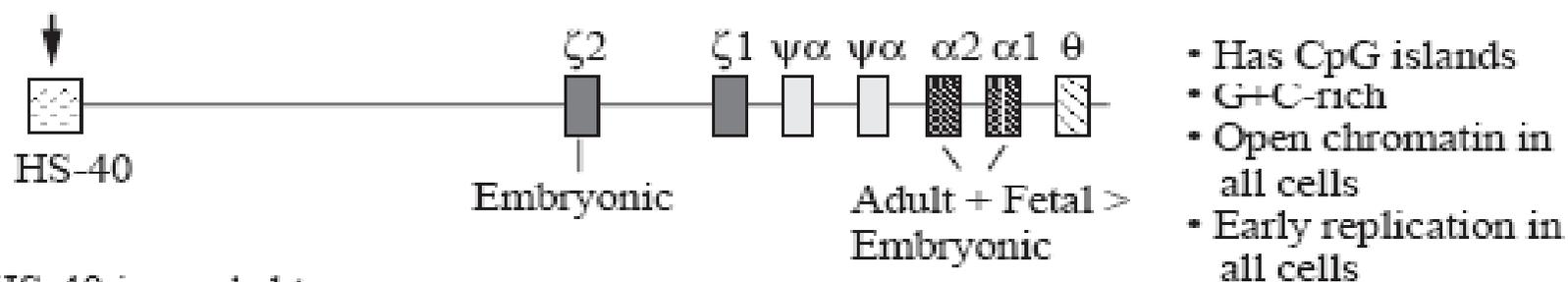
- 来源相同、结构相似、功能相关：基因家族
- 基因家族成员串联排列：基因簇
- 复制是新基因产生的重要方式
- 串联重复基因为进化提供素材
- 编码序列的改变、内含子数目增删、单个内含子序列长度的变化、内含子序列变化。





Locus control region is needed to:

- open a chromatin domain in erythroid cells
- express linked globin genes at a high level
- override position effects in transgenic mice



HS-40 is needed to:

- express linked globin genes at a high level
- override position effects in transgenic mice

## 二、血红蛋白结构及功能分析

# 研究历史

- 1851年 Otto Funke 获得氧合血红蛋白晶体
- 随后， Felix Hoppe-Seyler 描述了血红蛋白与氧的可逆结合过程
- 1959 年Max Perutz鉴定了其分子结构，并因此获得1962年的诺贝尔化学奖



## Otto Funke

Otto Funke ([October 27, 1828](#) - [August 17, 1879](#))  
was a German [physiologist](#) who was a native of [Chemnitz](#).

# Max Ferdinand Perutz,

(May 19, 1914, Vienna, Austria – February 6, 2002, Cambridge, UK) was an Austrian-British molecular biologist



At Cambridge he supervised the PhD work of **Francis Crick** and **James Watson** in the Cavendish Laboratory as they determined the structure of **DNA** in 1953

## 课题目的:

初步探索氧合曲线的成因及协同作用的分子机制  
揭示镰刀型细胞贫血症的蛋白质水平致病机制

- 使用工具: **Swiss-PdbViewer**

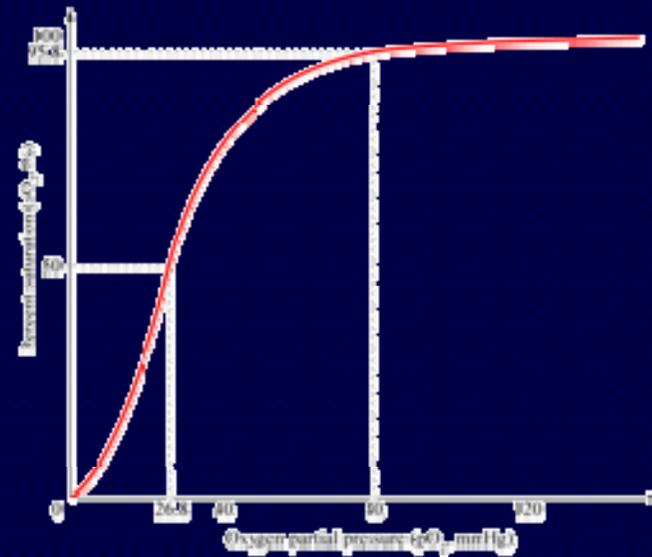
- 研究对象:

脱氧型人类变异血红蛋白结构 (2HBS),

脱氧型人类血红蛋白结构 (3HHB),

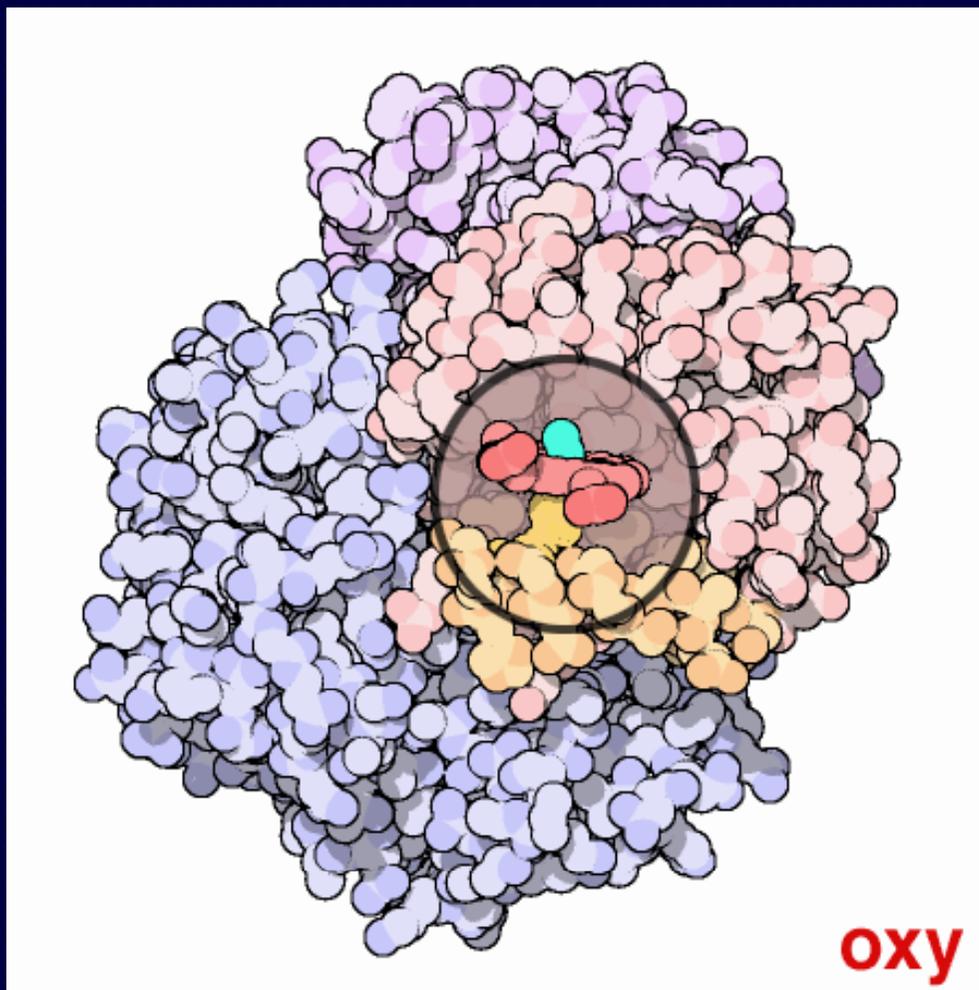
氧合型人类血红蛋白结构 (2DN1),

# 1、蛋白质结构与氧合曲线



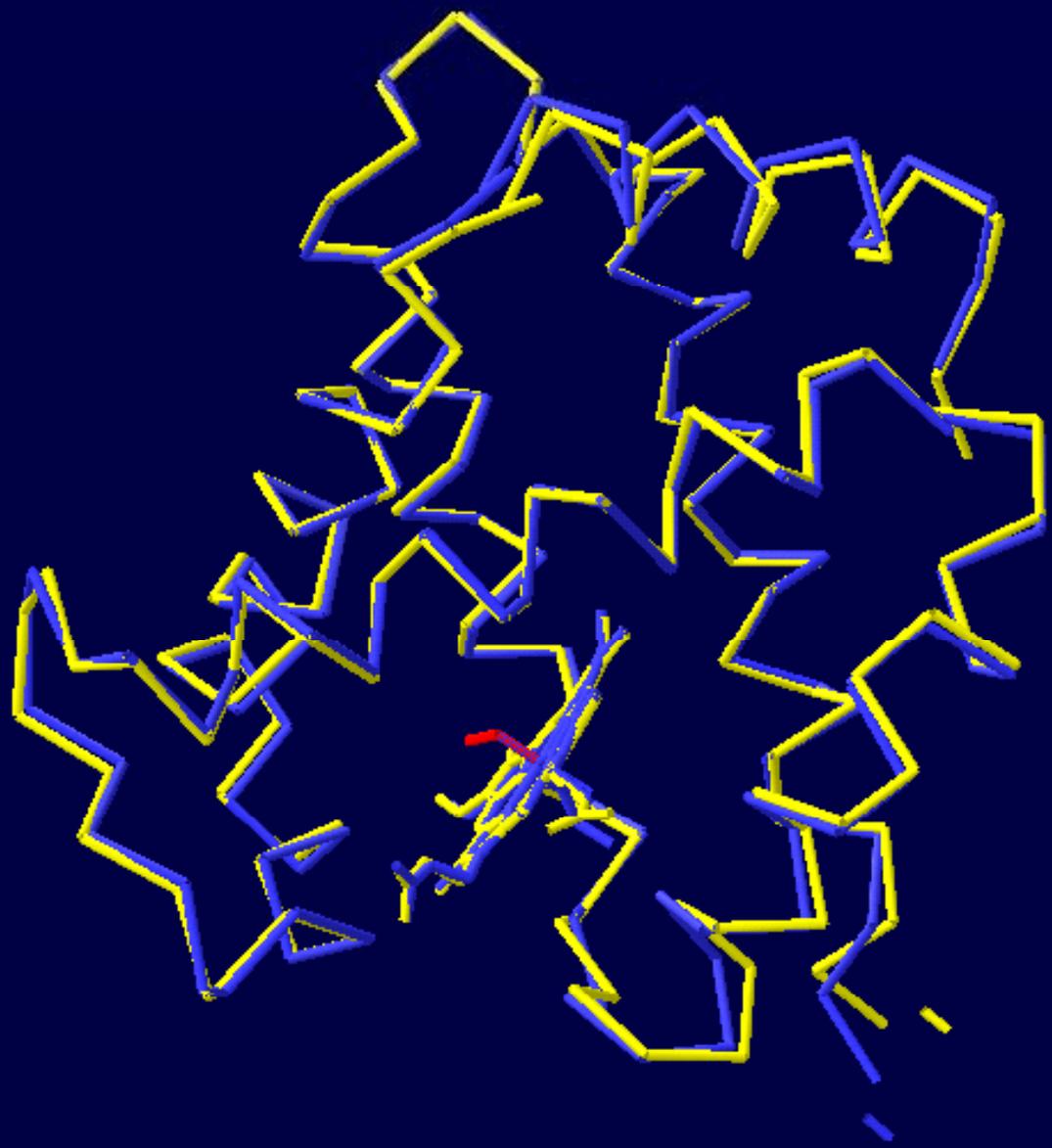
- 协同效应
- 首个亚基氧合困难
  - alpha亚基; beta亚基
- 一旦首个亚基氧合, 则利于其他亚基的构象变化

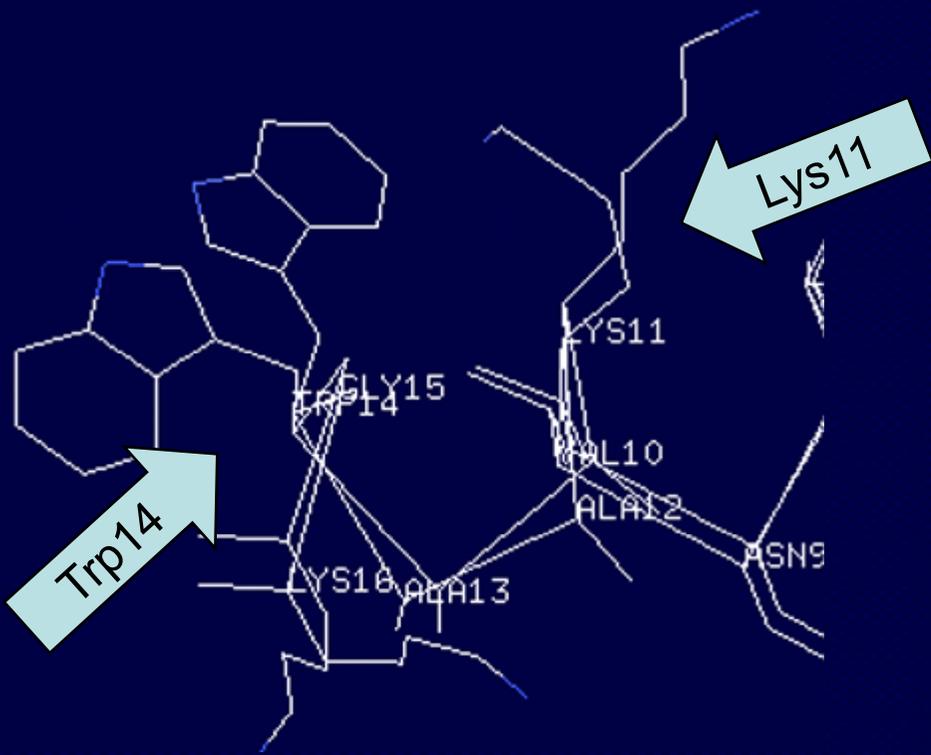


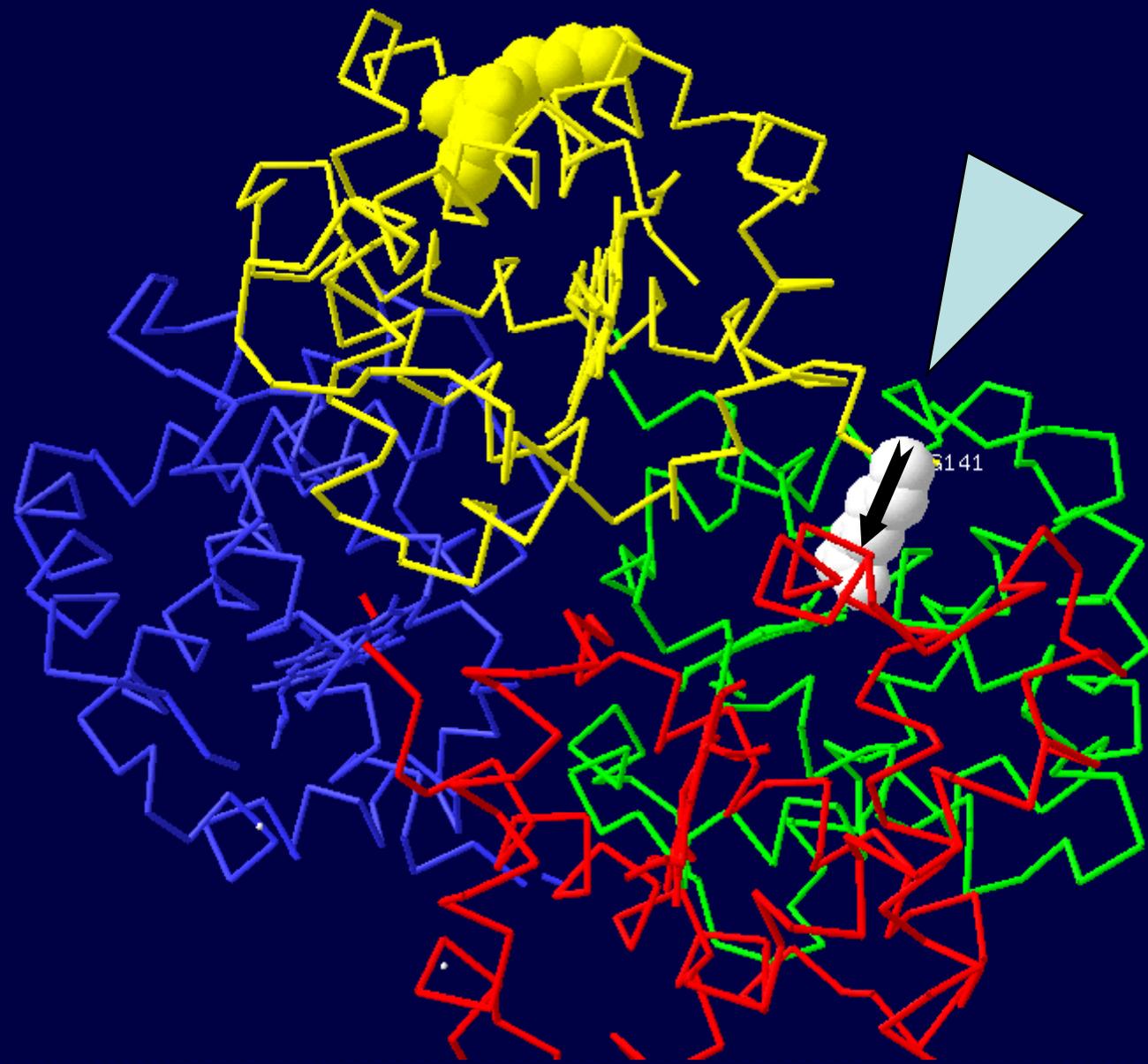


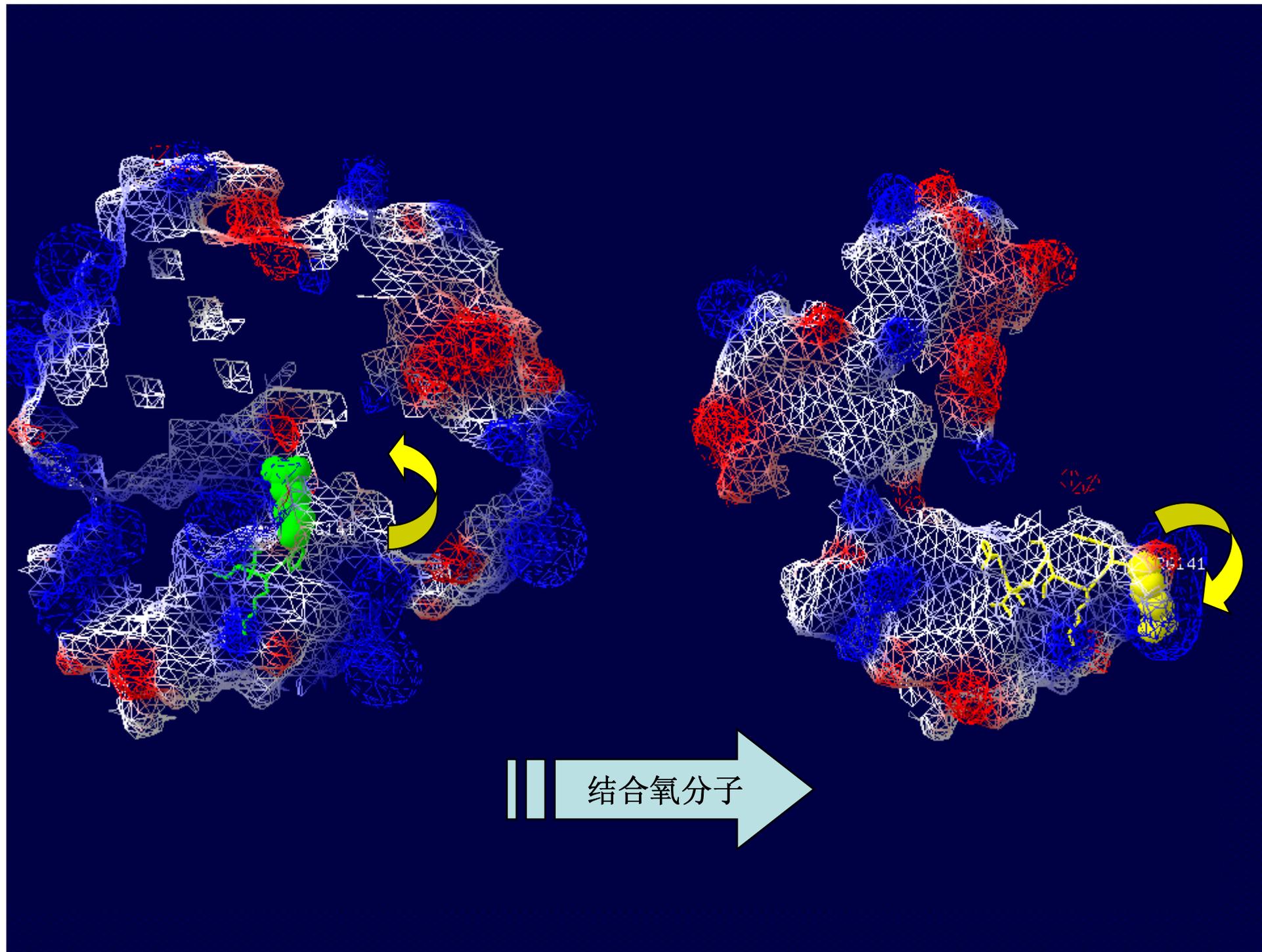
一样的结合解离造成整个血红  
蛋白结构的变化

alpha

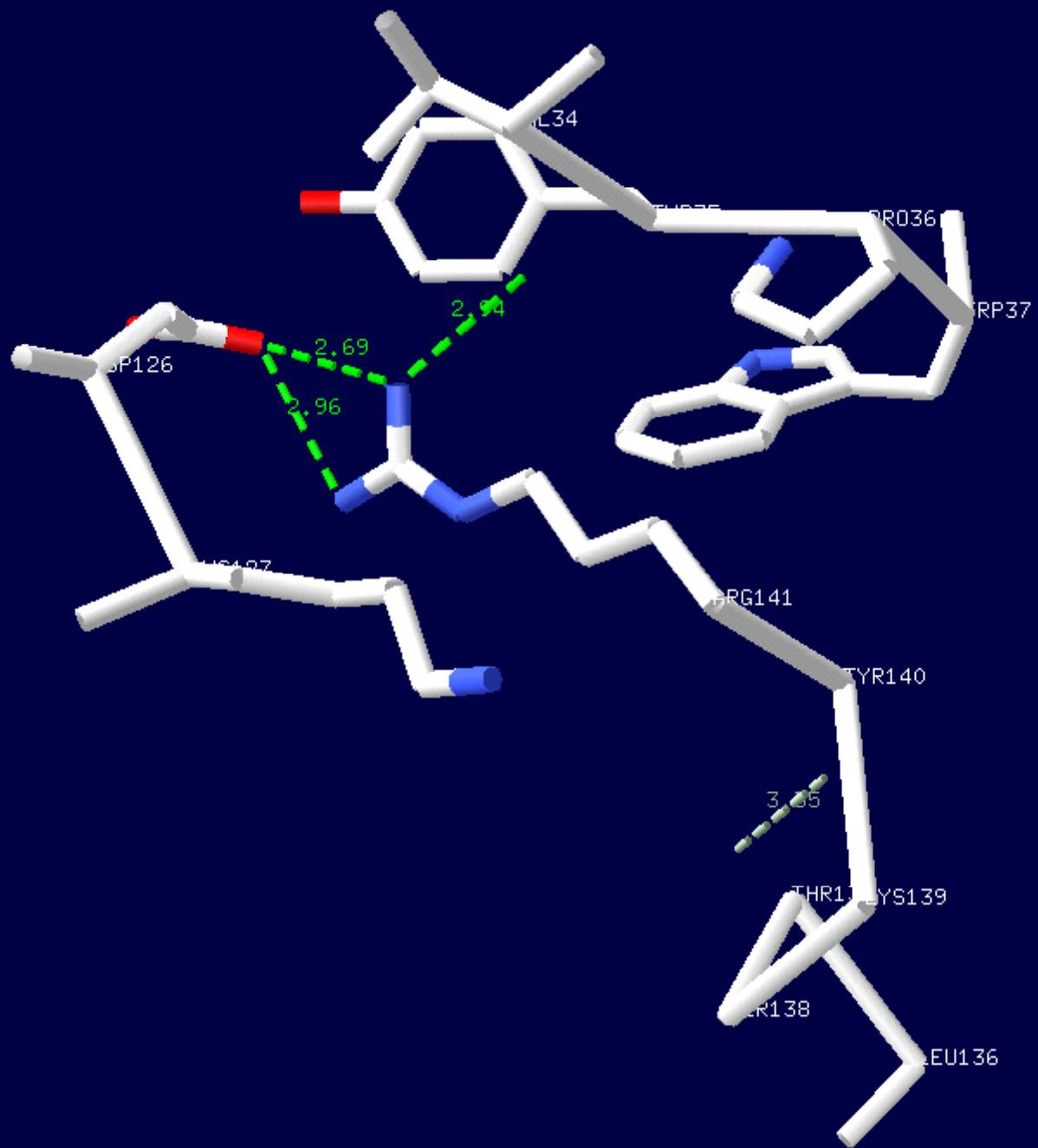


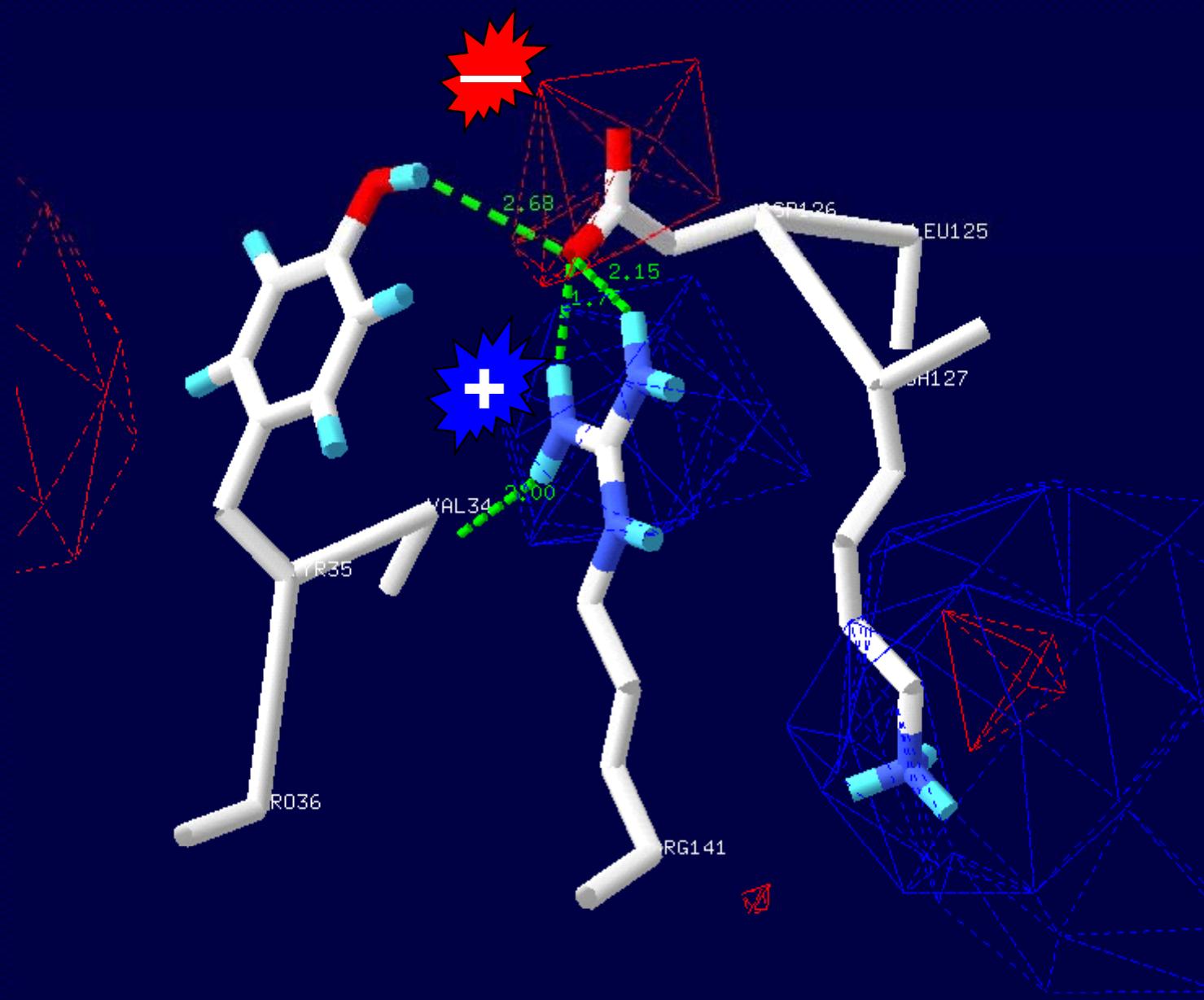








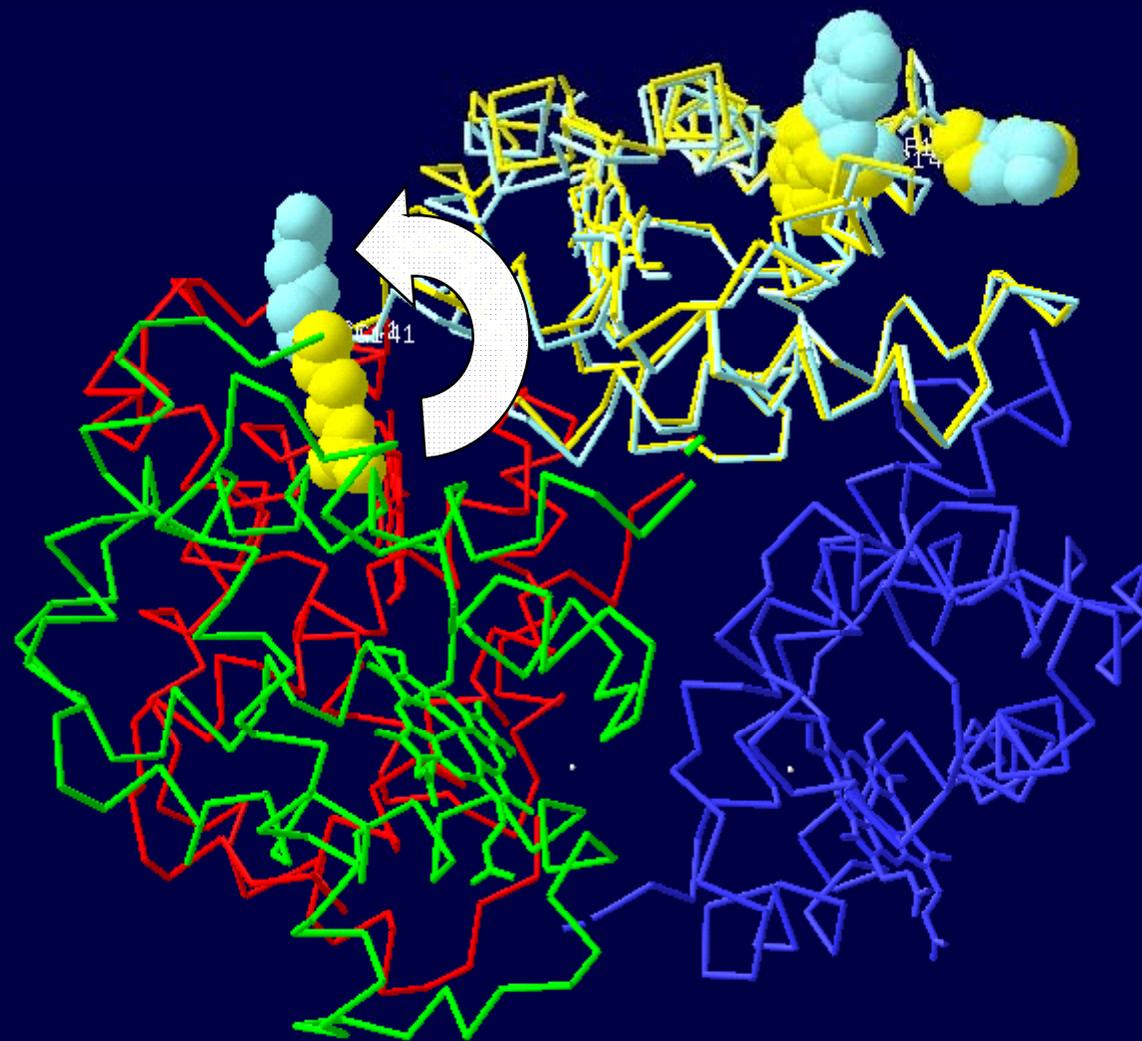




beta Try35

Arg141

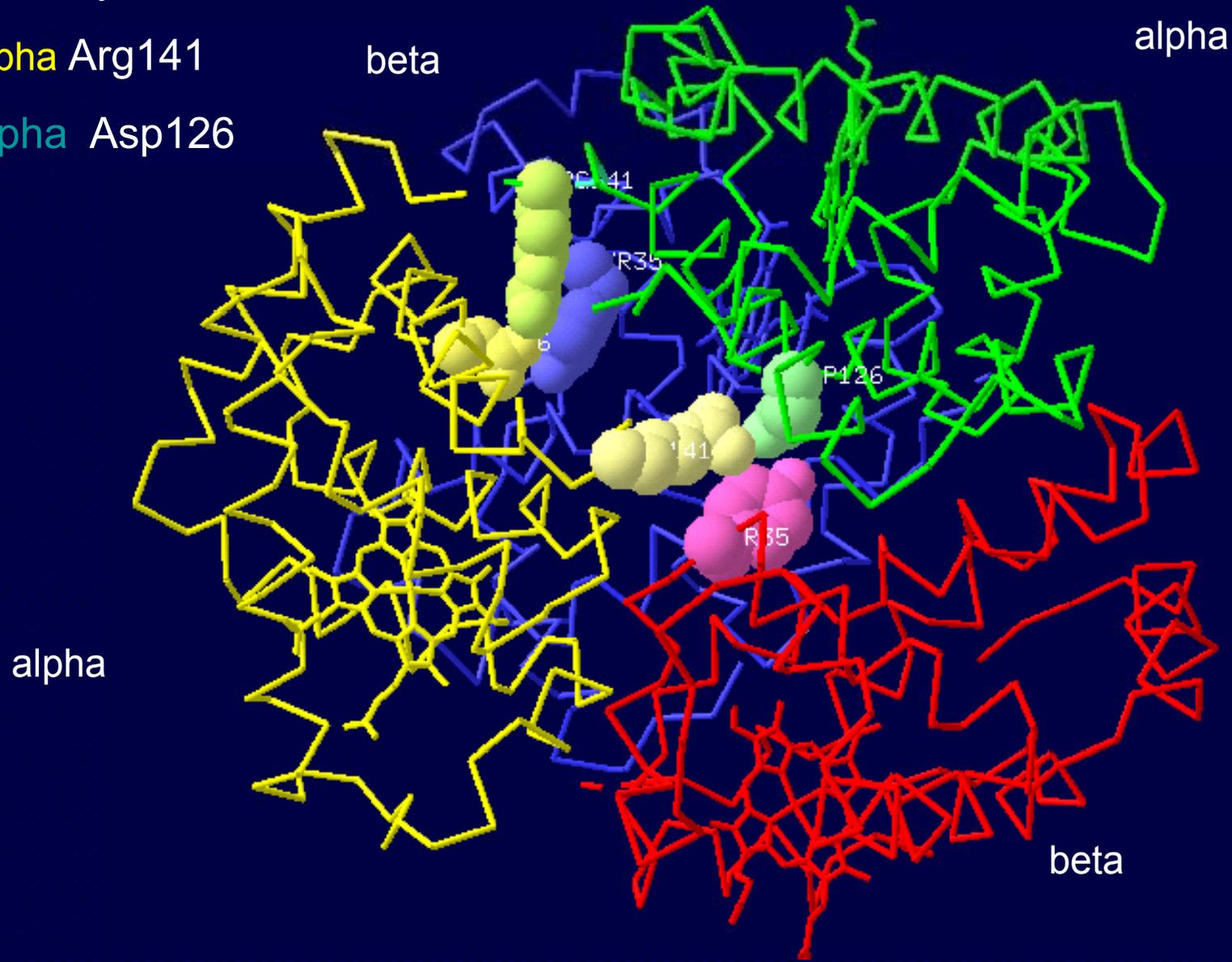
alpha Asp126



beta Try35

alpha Arg141

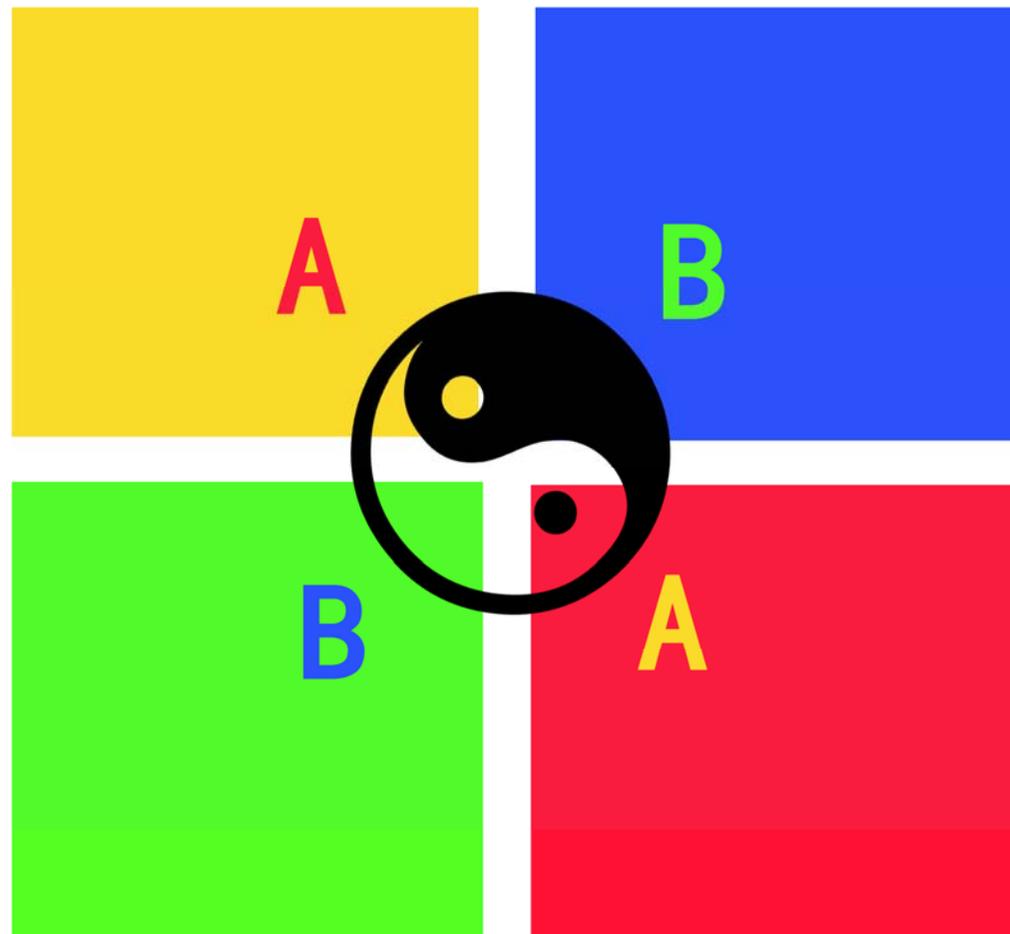
alpha Asp126



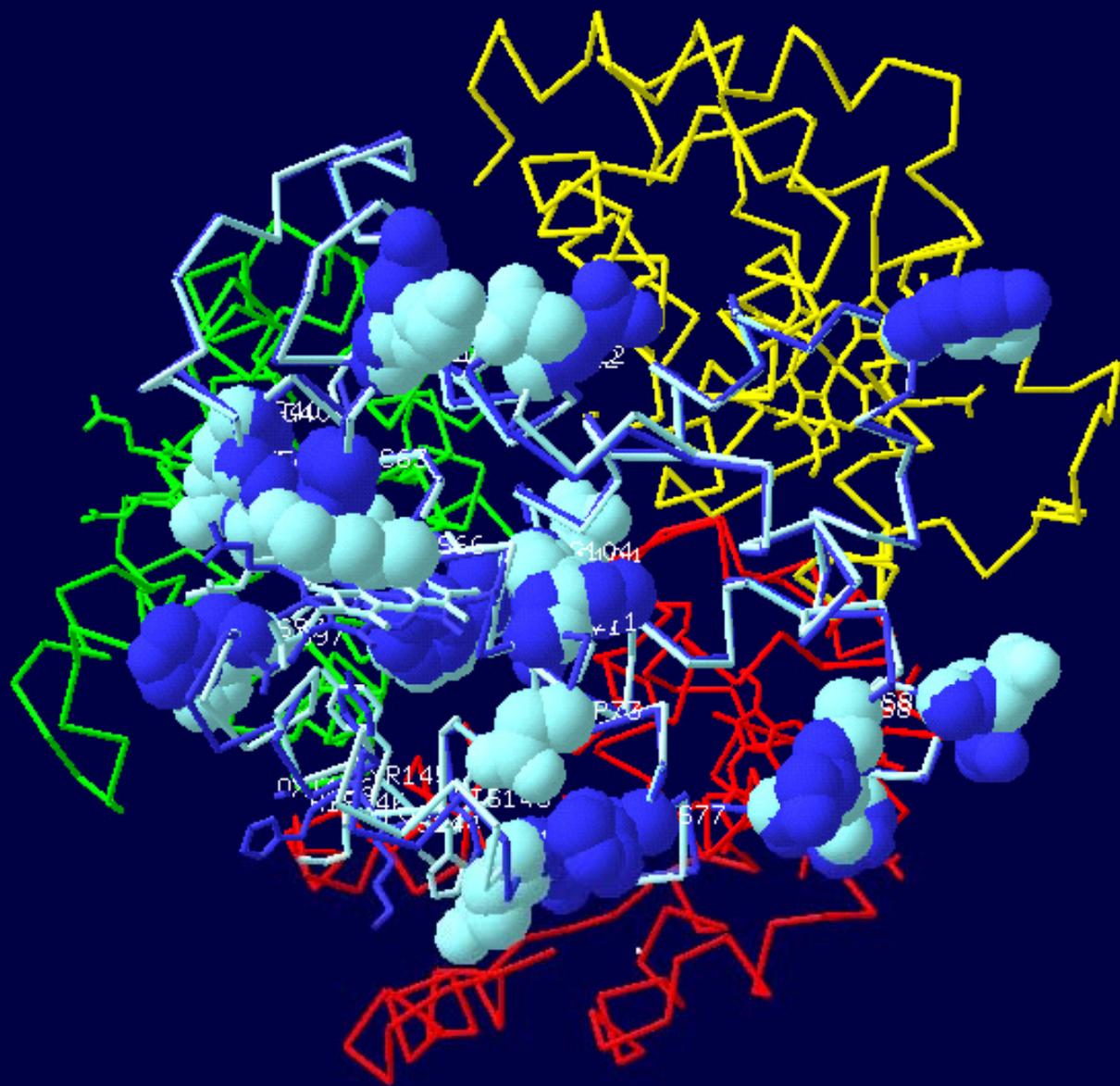
alpha

beta

氧合作用中alpha Arg141侧链位置发生重大变化  
alpha Arg141与相邻的beta Try35和alpha Asp126  
形成离子键，氧合作用必须破坏之

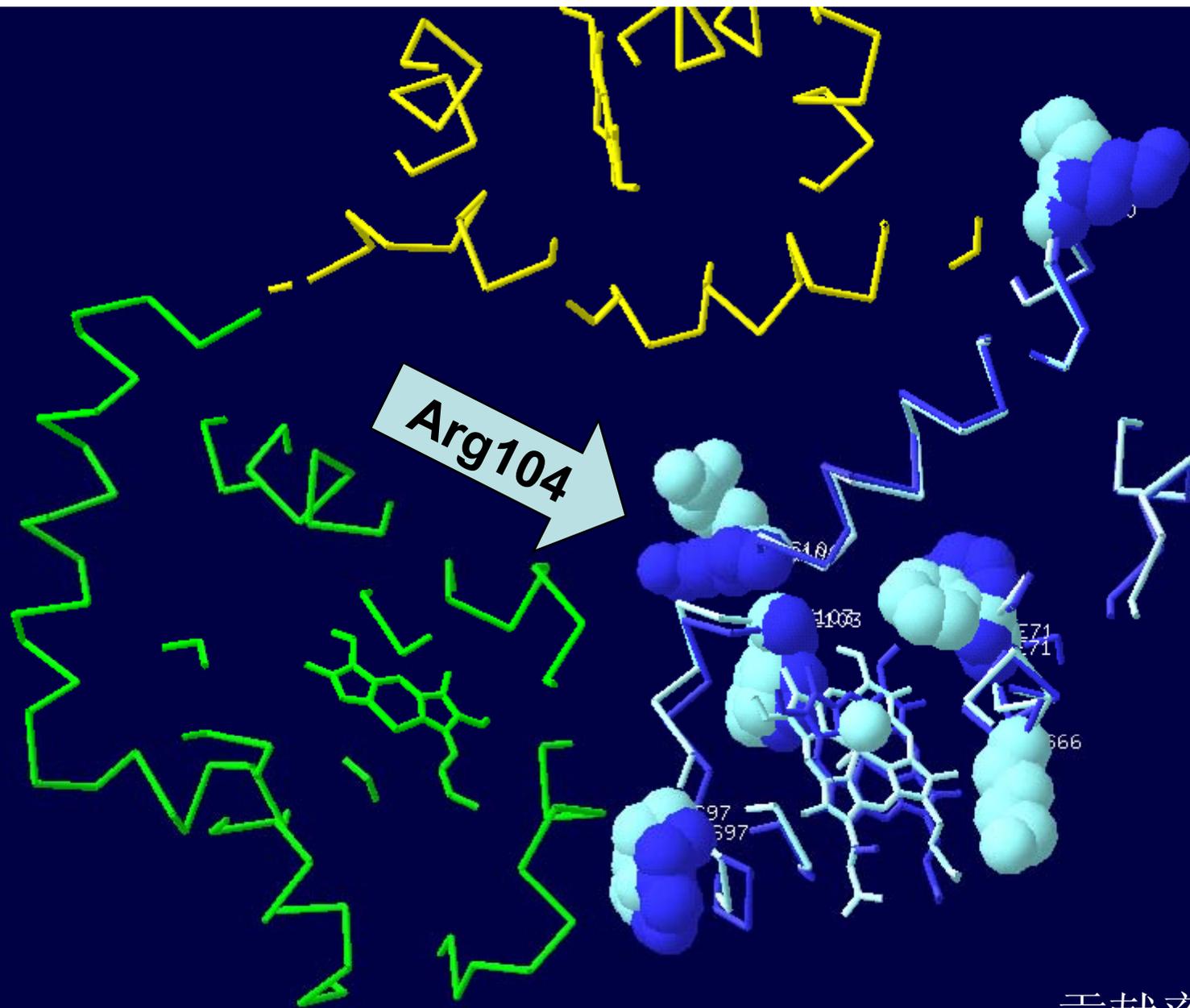


beta

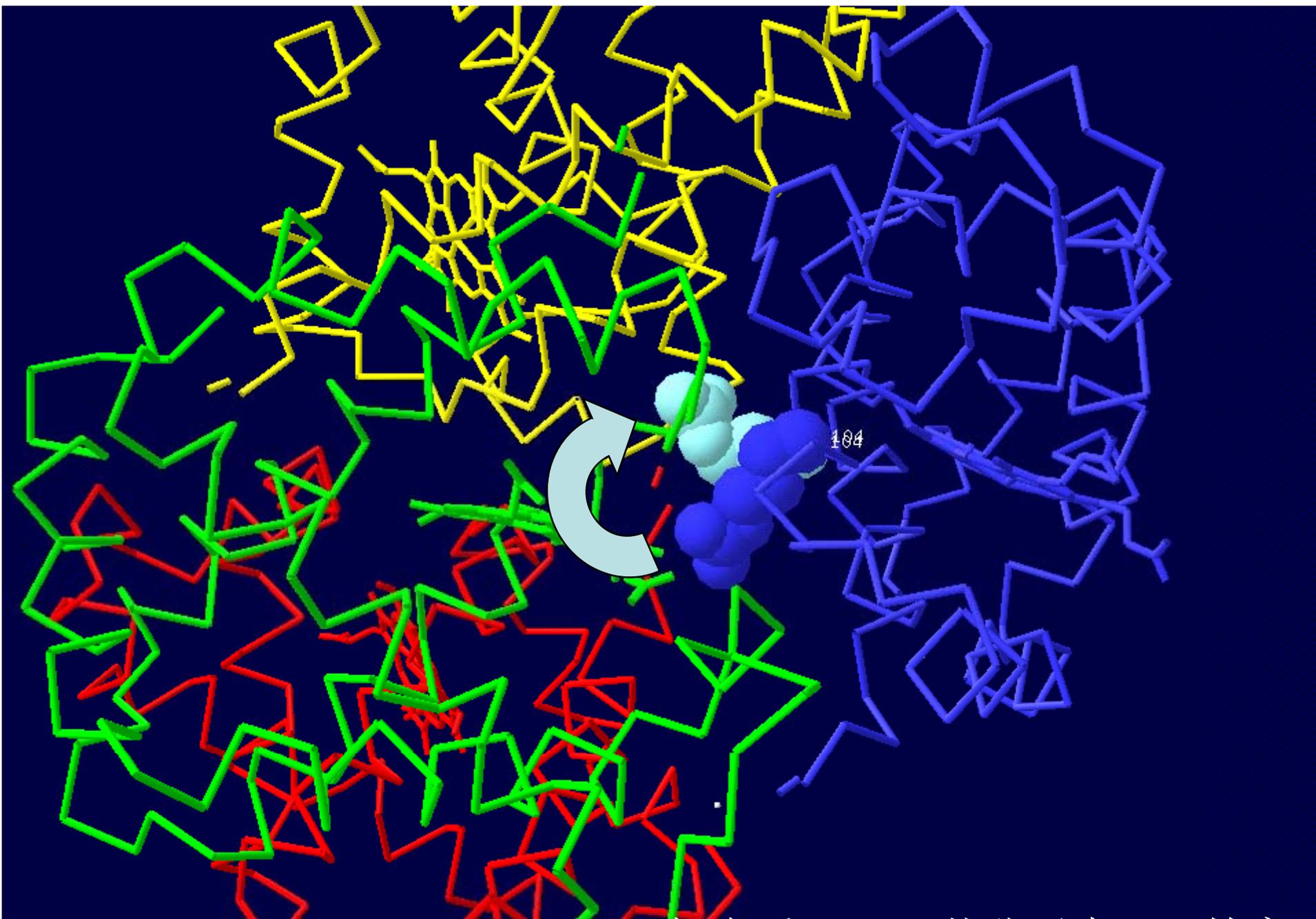


- His2
- Glu6
- Lys8
- Glu22
- Arg40
- Phe41
- Lys61
- Lys66
- Phe71
- Asp73
- Lys82
- His97
- Lys99
- Phe103
- Arg104**
- Lys120

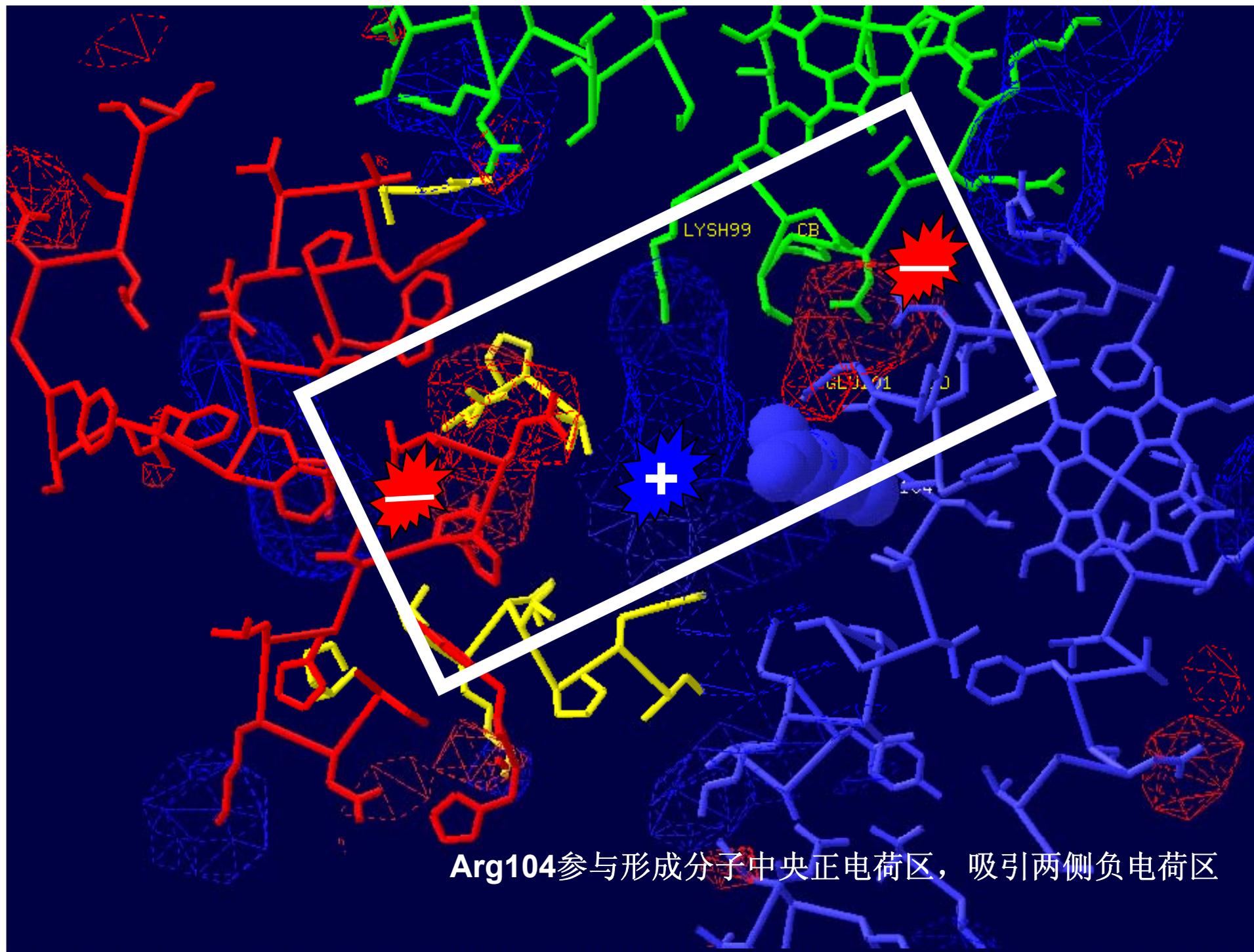
情况比较复杂

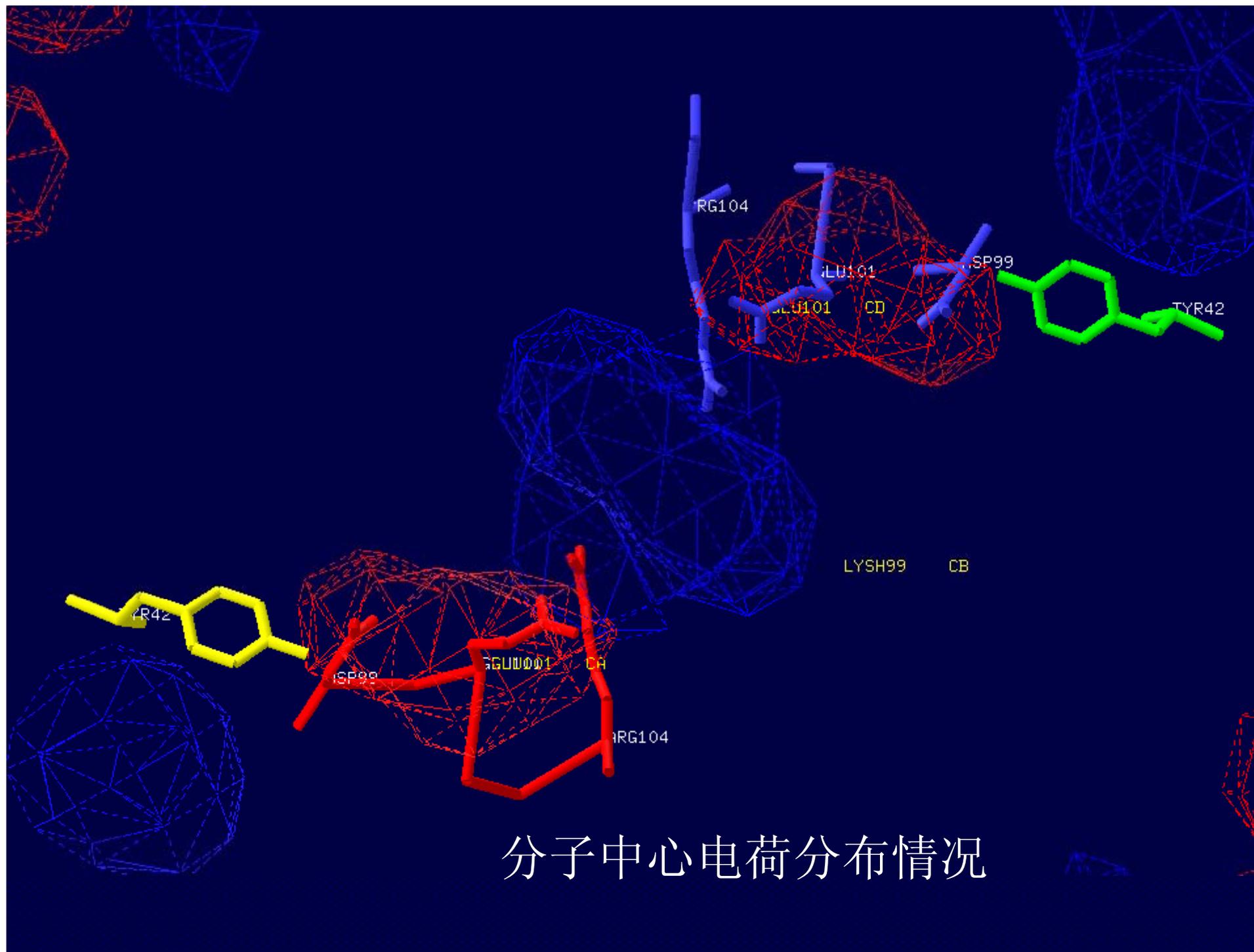


贡献率不同



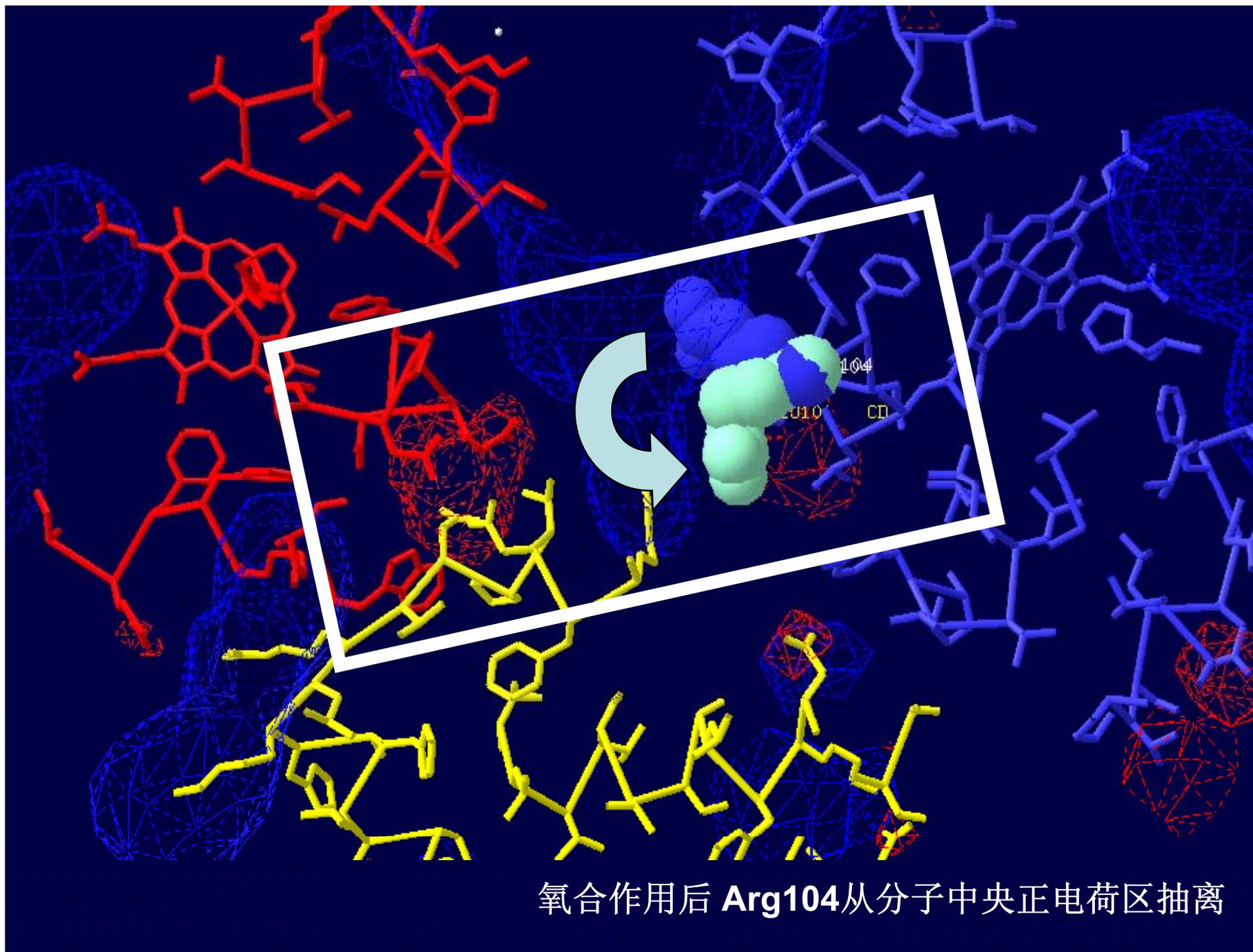
氧合后Arg104从分子中心“抬离”

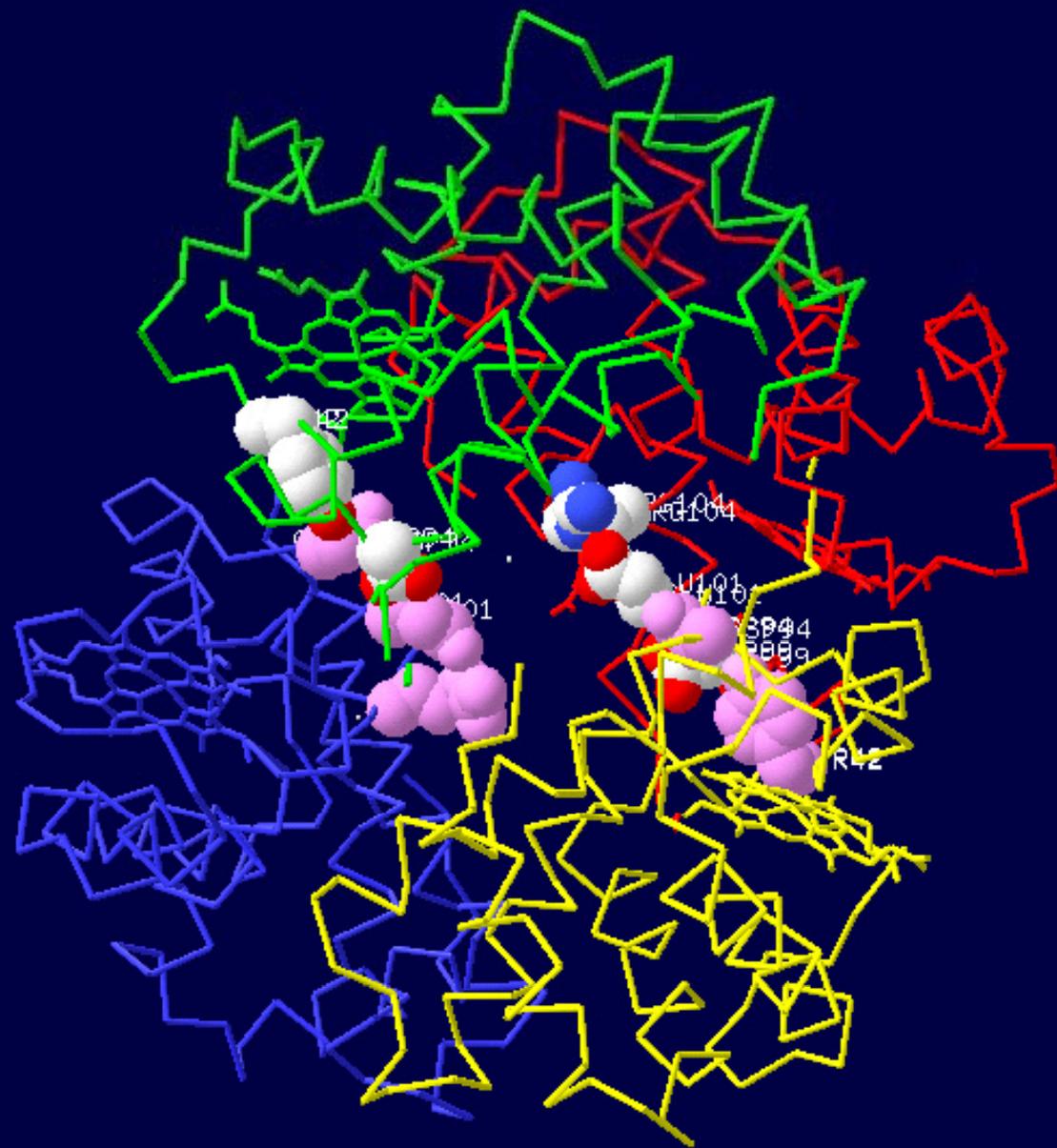




分子中心电荷分布情况





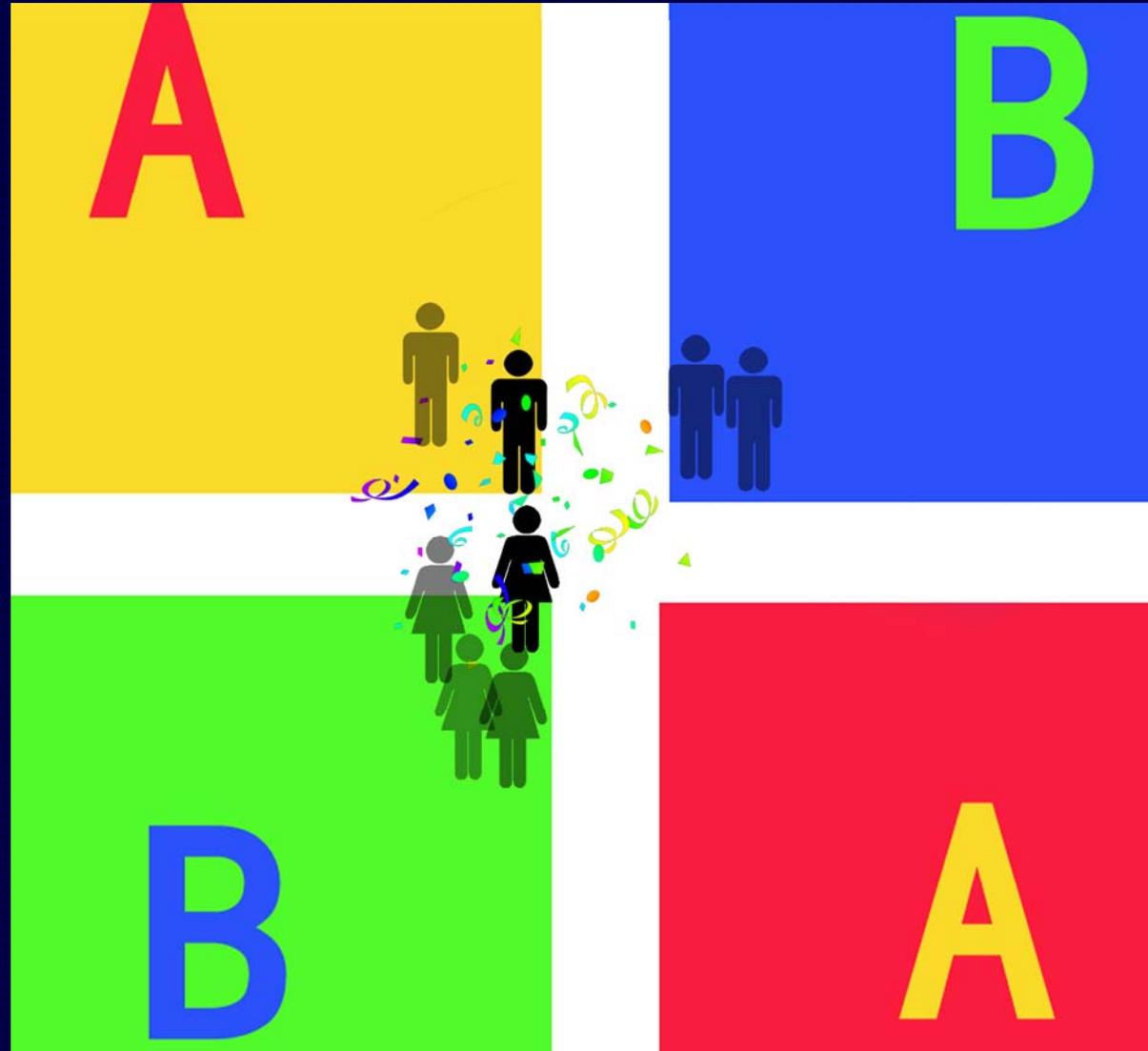


Beta Arg104参与形成分子中央正电荷区，吸引两侧负电荷区：beta -Glu101、Asp99 /alpha -Asp94、Tyr42  
首次氧合作用必须克服此电荷吸引作用。

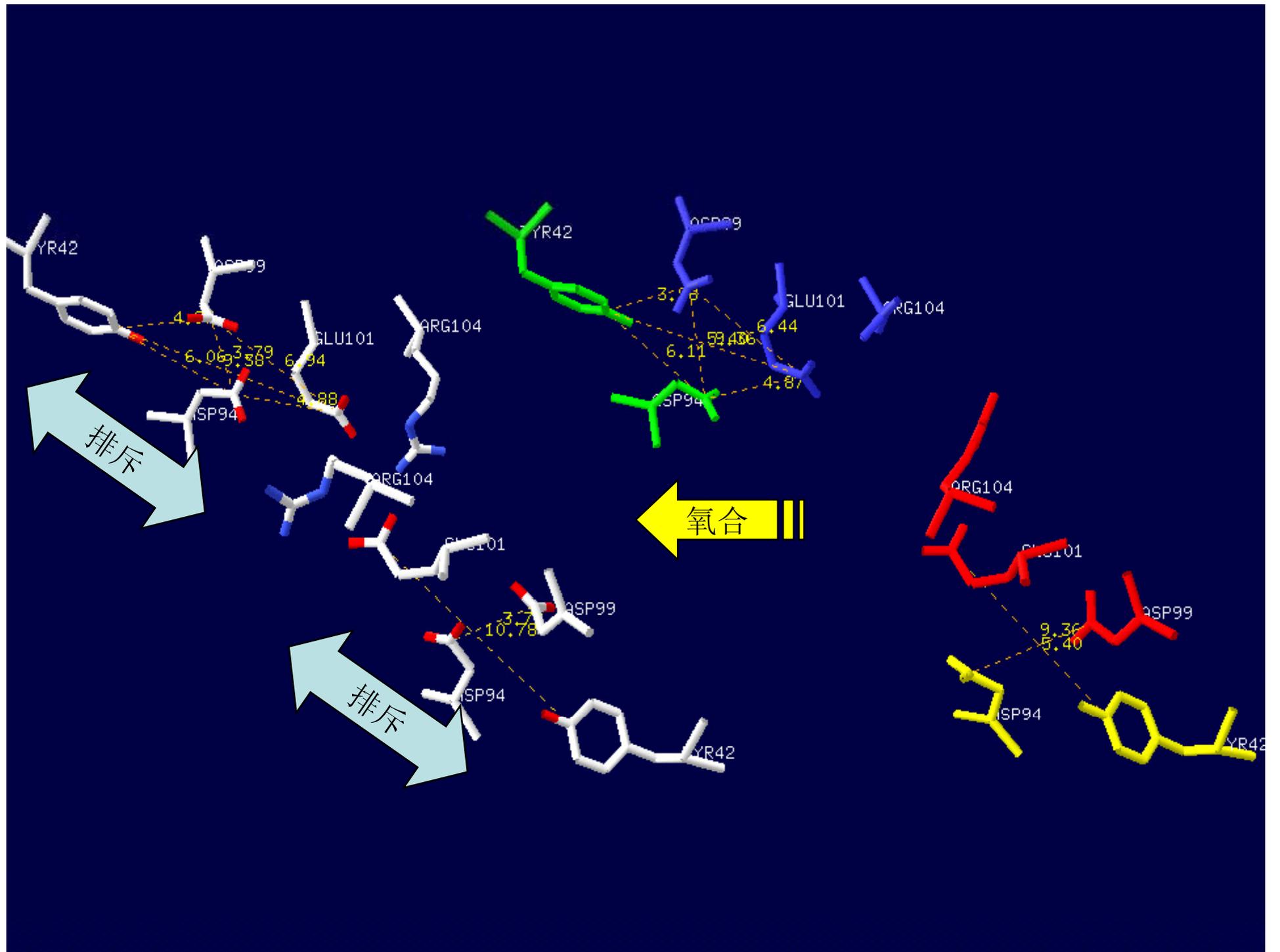


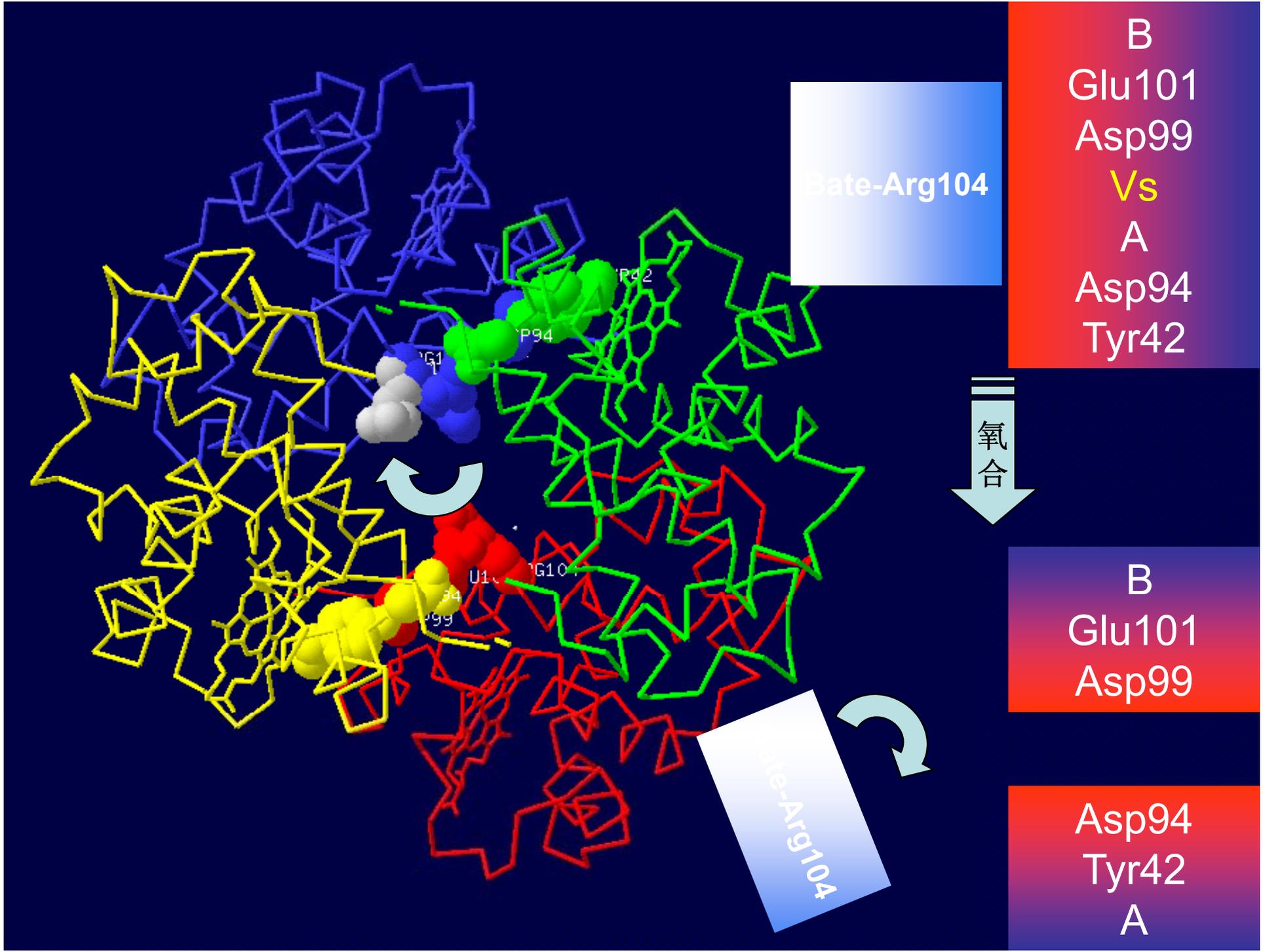
刘三姐

隔江对歌

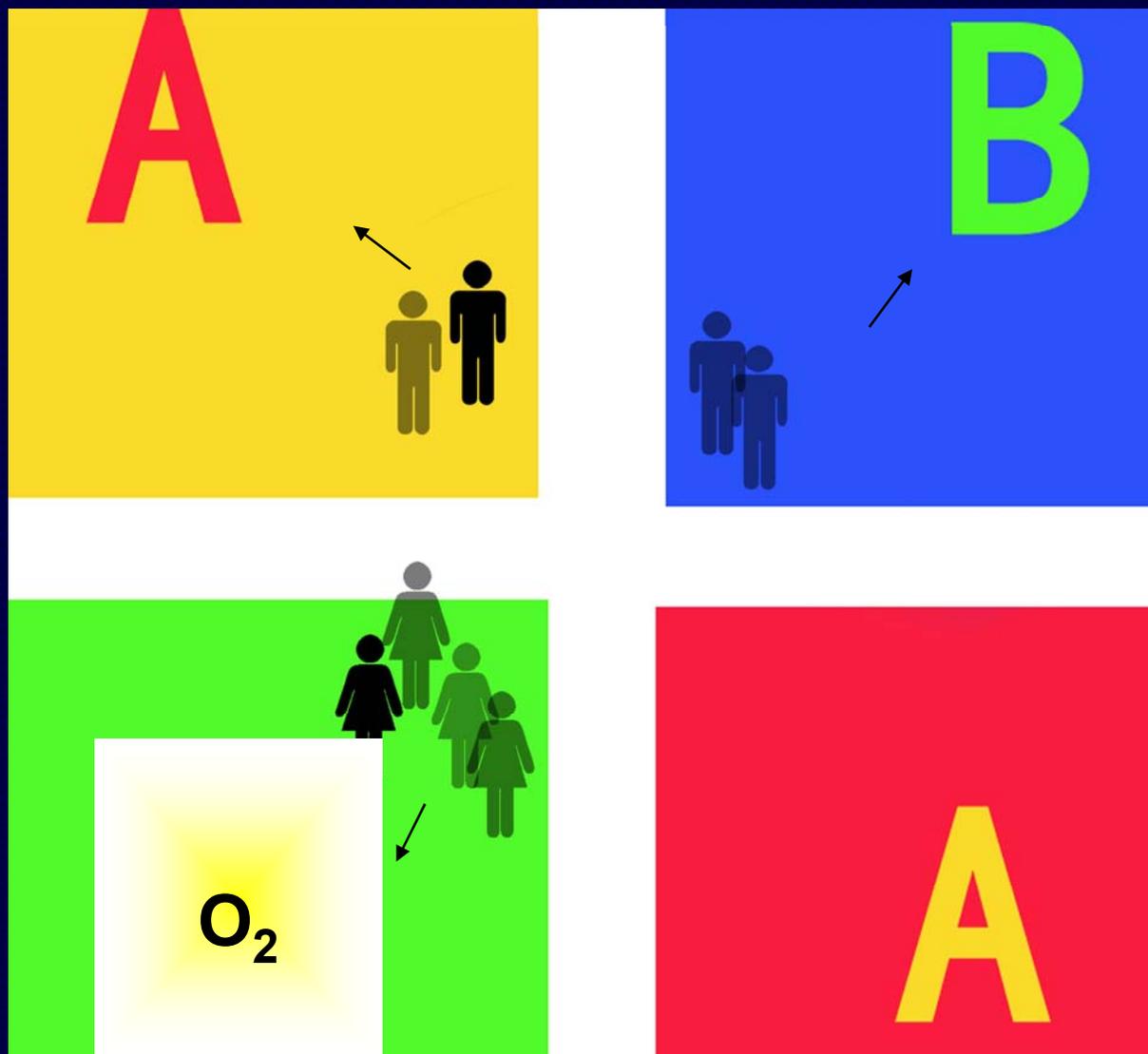


Beta亚基氧合促使其他亚基的结构变化





氧合作用下，Beta Arg104从分子中央正电荷区撤离，  
导致负电荷区变形，引发其他亚基的构象变化



灯都点了，  
该回家了！

# 斑头雁、灰雁和人血红蛋白比较 与氧合特征

兰军 李瑶 唐然 杨萍

- 斑头雁(*Anser indicus*)生活在海拔4000-6000 米的中国青海湖区域，它们能忍受高海拔的缺氧环境，每年深秋经过喜马拉雅山(海拔约9000 米)迁徙到印度。
- 灰雁与斑头雁亲缘关系很近，长年生活在印度平原，但是它们却不能承受缺氧的环境。

# 斑头雁和灰雁血红蛋白的序列比对结果

LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
141	711.0	138/141 (97.9%)	138/141 (97.9%)	0/141 (0.0%)

1FAWA	1	VLSAADKTNVKGVFSKIGGHAE EYGAETLERMFTAYPQTKTYFPHFDLQH	50
1A4FA	1	VLSAADKTNVKGVFSKISGHAE EYGAETLERMFTAYPQTKTYFPHFDLQH	50
1FAWA	51	GSAQIKAHGKKVAAALVEAVNHIDDIAGALSKLSDLHAQKLRVDPVNFKF	100
1A4FA	51	GSAQIKAHGKKVAAALVEAVNHIDDIAGALSKLSDLHAQKLRVDPVNFKF	100
1FAWA	101	LGHCFLVVVAIHHP SALTAEVHASL DKFLCAVGT VLTAKYR	141
1A4FA	101	LGHCFLVVVAIHHP SALTAEVHASL DKFLCAVGT VLTAKYR	141

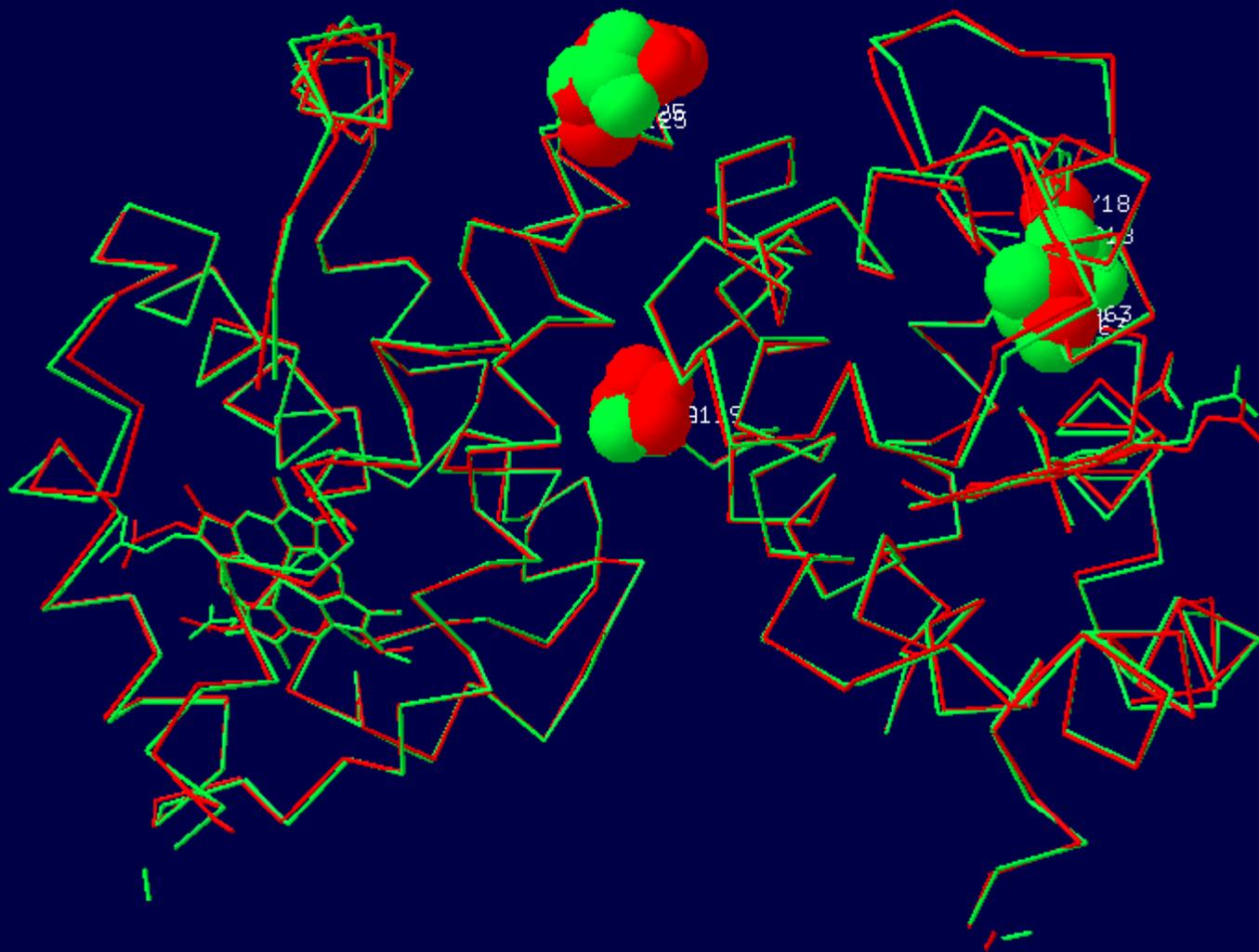
  

LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
146	763.0	145/146 (99.3%)	146/146 (100.0%)	0/146 (0.0%)

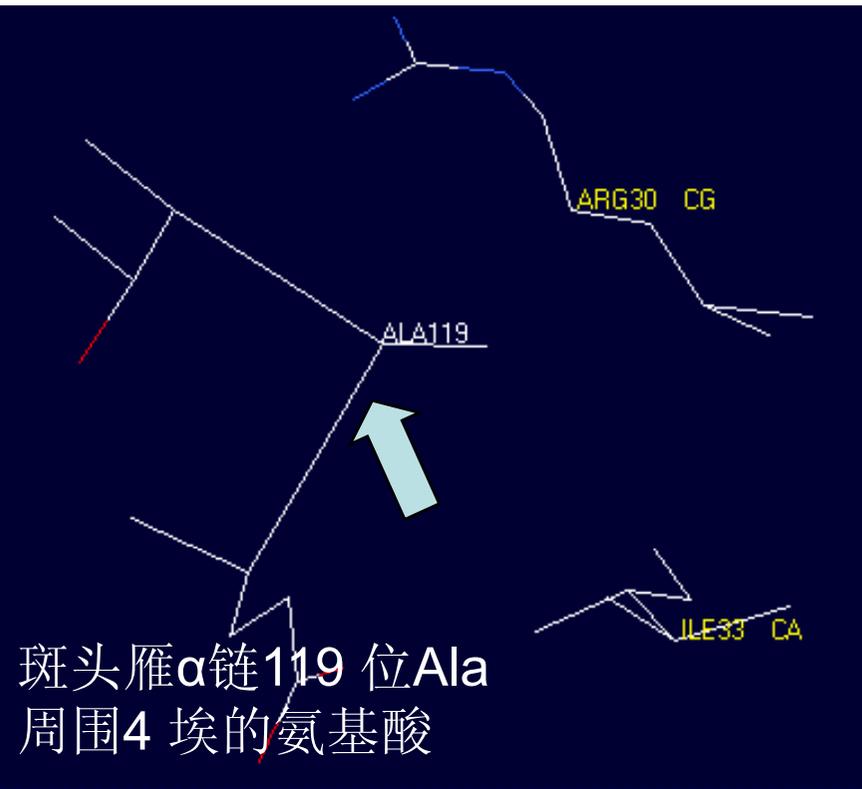
1FAWB	1	VHWSAE EKQLITGLWGKVNVDCCGA EALARLLIVYPWTQRFFSSFGNLSS	50
1A1FB	1	VHWSAE EKQLITGLWGKVNVDCCGA EALARLLIVYPWTQRFFSSFCNLSS	50
1FAWB	51	PTAILGNPMVFAHGKKVLT SFGDAVKNLDNIKNTFAQLSELHCDKLHVDP	100
1A4FB	51	PTAILGNPMVFAHGKKVLT SFGDAVKNLDNIKNTFAQLSELHCDKLHVDP	100
1FAWB	101	ENFRLLGDILIIIVLAAHF AKEFTFE CQAAMQKLV RVVAHALARKYH	146
1A4FB	101	ENFRLLGDILIIIVLAAHF AKEFTFE CQAAMQKLV RVVAHALARKYH	146

斑头雁和灰头雁血红蛋白仅有4个氨基酸的差异



斑头雁 $\alpha$ 链119位Ala  $\beta$ 链125位Asp  
灰雁 Pro Glu  
它们位于血红蛋白 $\alpha$ 链和 $\beta$ 链的结合处

灰雁 $\alpha$ 链119位Pro周围4埃的氨基酸

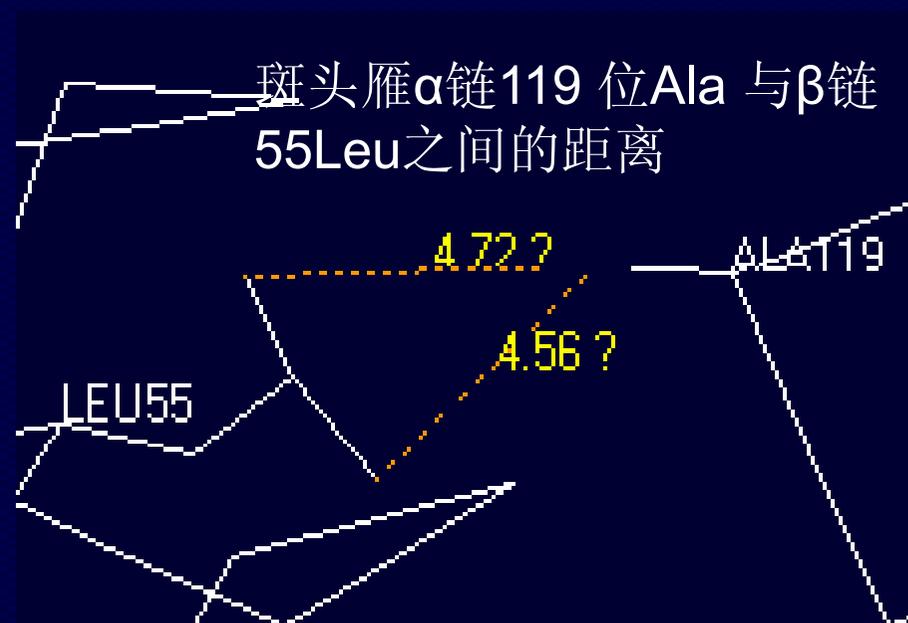


斑头雁 $\alpha$ 链119位Ala周围4埃的氨基酸

灰雁 $\alpha$ 链119位Pro与 $\beta$ 链55Leu之间的距离



斑头雁 $\alpha$ 链119位Ala与 $\beta$ 链55Leu之间的距离



# 人和斑头雁血红蛋白的序列比对

Pairwise Alignment Result

LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
142	515.0	98/142 (69.0%)	109/142 (76.8%)	0/142 (0.0%)

HBA_HUMAN	1	MVLSPADKTNVKAAGKVGAGHAGEYGAELERMFLSFPTTKTYFPHF <del>DL</del> S	50
		.             . . . :   : . .     .         .         : :   .             .	
HBA_ANSIN	1	MVLSAAADKTNVKGVFSKISGHAEEYGAETLERMFTAYPQTKTYFPHF <del>D</del> LQ	50
HBA_HUMAN	51	HGSAQVXGHHGKKVADALTNVAHVDMPNALSALS <del>DL</del> HAHKL <del>R</del> VD <del>P</del> VNFK	100
		:   .         . .     . .     .   :     : . .       .	
HBA_ANSIN	51	HGSAQIKAHGKKVVAALVEAVNHIDDIAGALS <del>KL</del> SDLHAQKL <del>R</del> VD <del>P</del> VNFK	100
HBA_HUMAN	101	LLSHCLLVTLAAHLFAEFTPAVHASL <del>D</del> KFLASVSTVLT <del>S</del> KYR	142
		.   .     .     :   .   .   : . .   . .                 . :   .         :	
HBA_ANSIN	101	FLGHCF <del>L</del> VVVAIHHFSALTAEVHASL <del>D</del> KFLCAVGT <del>V</del> LTA <del>K</del> YR	142

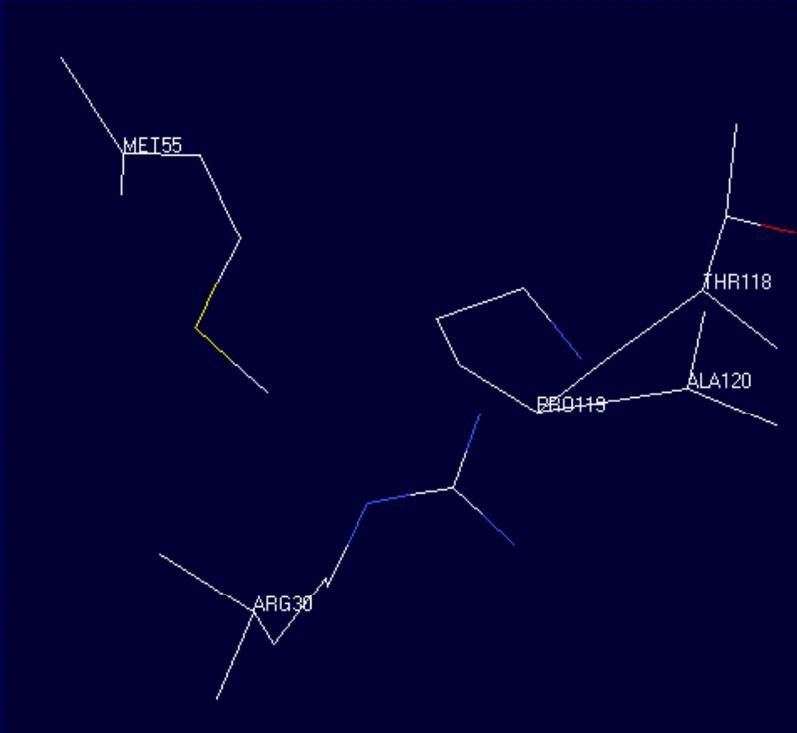
Pairwise Alignment Result

LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
147	549.0	101/147 (68.7%)	120/147 (81.6%)	1/147 (0.7%)

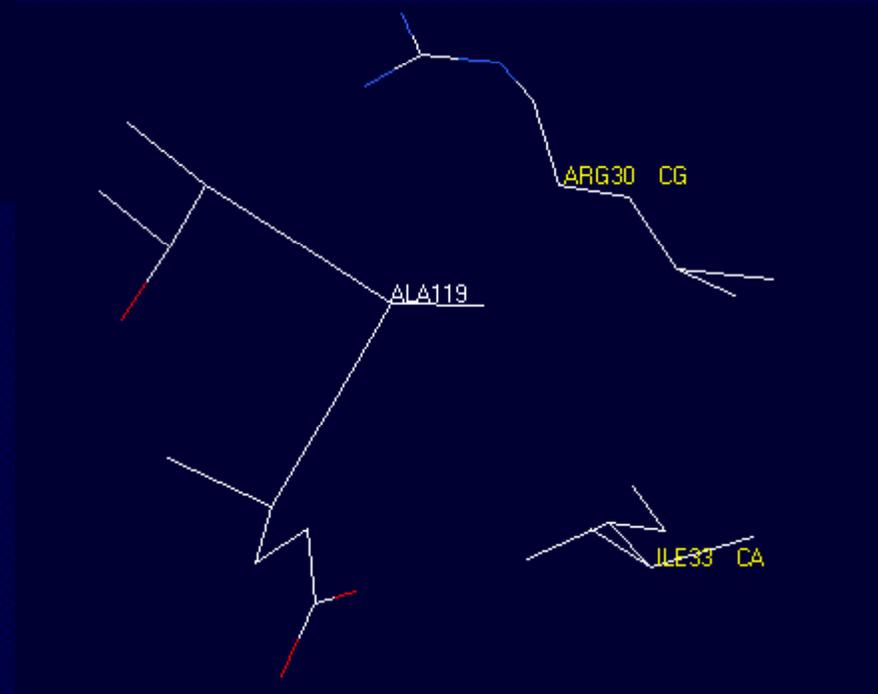
  

HBB_ANSIN	1	-VHWSAEEKQLITGLWQKVNVD <del>CG</del> AELARLLIVYPWTQRFFSS <del>F</del> GNLS	49
		. . :       . . :   .             . . :   .       .     :                 .       :	
HBB_HUMAN	1	MVHLTP <del>EE</del> KSAVTA <del>L</del> WQKVNVD <del>EV</del> GG <del>E</del> ALGRLLVVYPWTQRFF <del>ES</del> FDLS	50
HBB_ANSIN	50	SPTAILGNPMVRAHGKKVLTSGDAVKNL <del>DN</del> IKNTFAQLSELH <del>CD</del> KLHVD	99
		:   .   : :       . . :                 . . :   . . . . :       :   .	
HBB_HUMAN	51	TPDAVMGNPKVKAHGKKV <del>L</del> GAFSDGLAHL <del>DN</del> LKGT <del>F</del> ATLSELH <del>CD</del> KLHVD	100
HBB_ANSIN	100	PENFRLLGDILIIIVLAAHFAKEFT <del>PD</del> CQA <del>AW</del> QKLV <del>RV</del> VAAHAL <del>AR</del> KYH	146
		: :     .       .             . .       :     :   . .     :	
HBB_HUMAN	101	PENFRLLGNV <del>L</del> VCVLAHHFGKEFT <del>PP</del> VQA <del>AY</del> QK <del>V</del> VAGVAN <del>AL</del> AH <del>AR</del> KYH	147

## 人 $\alpha$ 链119位Pro 周围4 埃的氨基酸

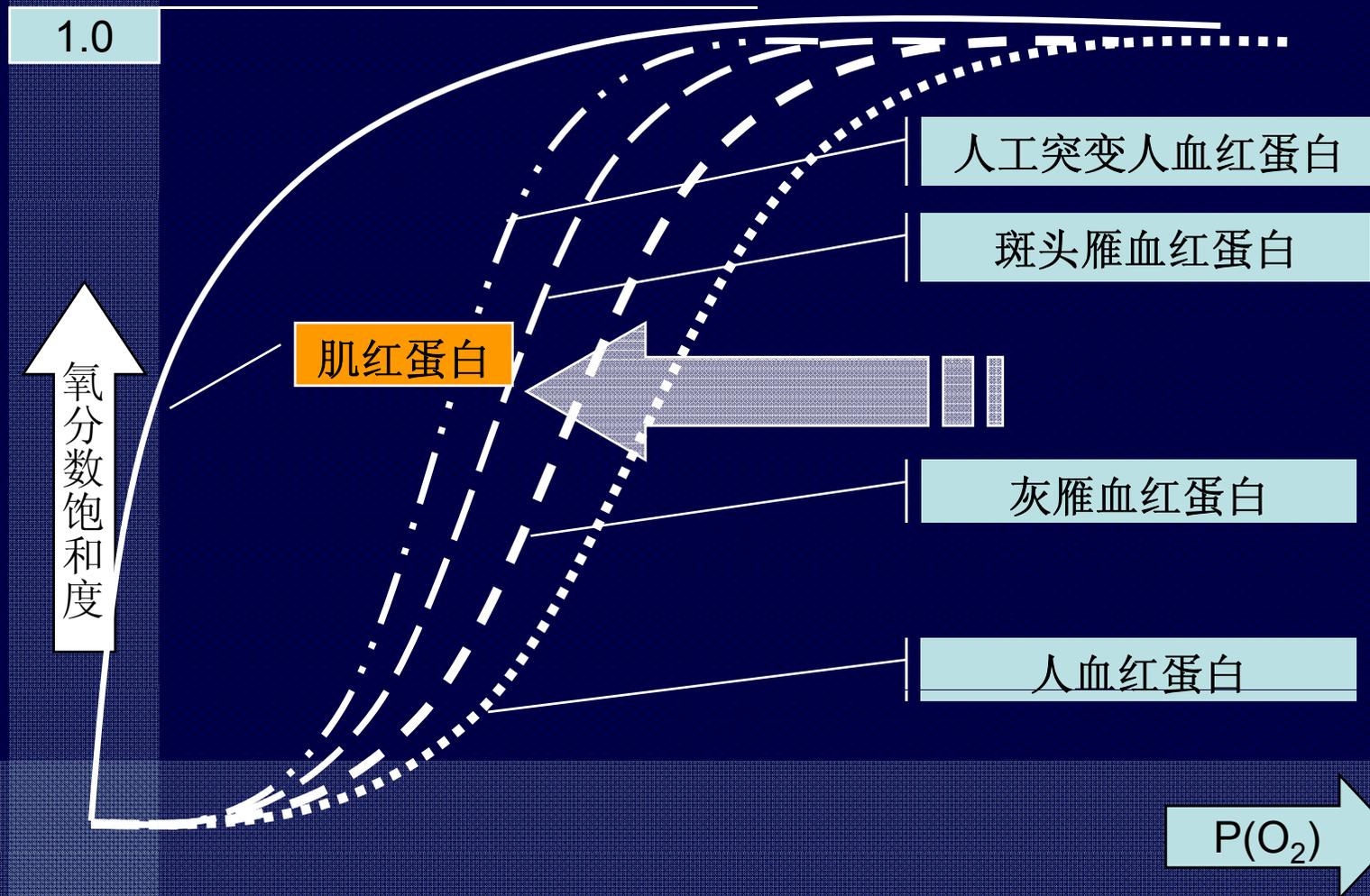


## 斑头雁 $\alpha$ 链119位Ala 周 围4 埃的氨基酸



- 与人和灰雁比较，斑头雁血红蛋白 $\alpha$ 链119位Ala使亚基间距离减小，导致分子疏松、亚基间牵制作用弱，从而更易结合氧气分子。推测其氧合曲线趋于平缓，这符合斑头雁在高原缺氧情况下结合氧气的需求。
- $\alpha$ -119 在血红蛋白氧亲和力上起到了非常重要的作用。因此可以通过改变这一残基来提高血红蛋白的氧亲和力。

# $\alpha$ 链119位与氧合曲线关系



# H<sup>+</sup>、CO<sub>2</sub>促进氧的释放

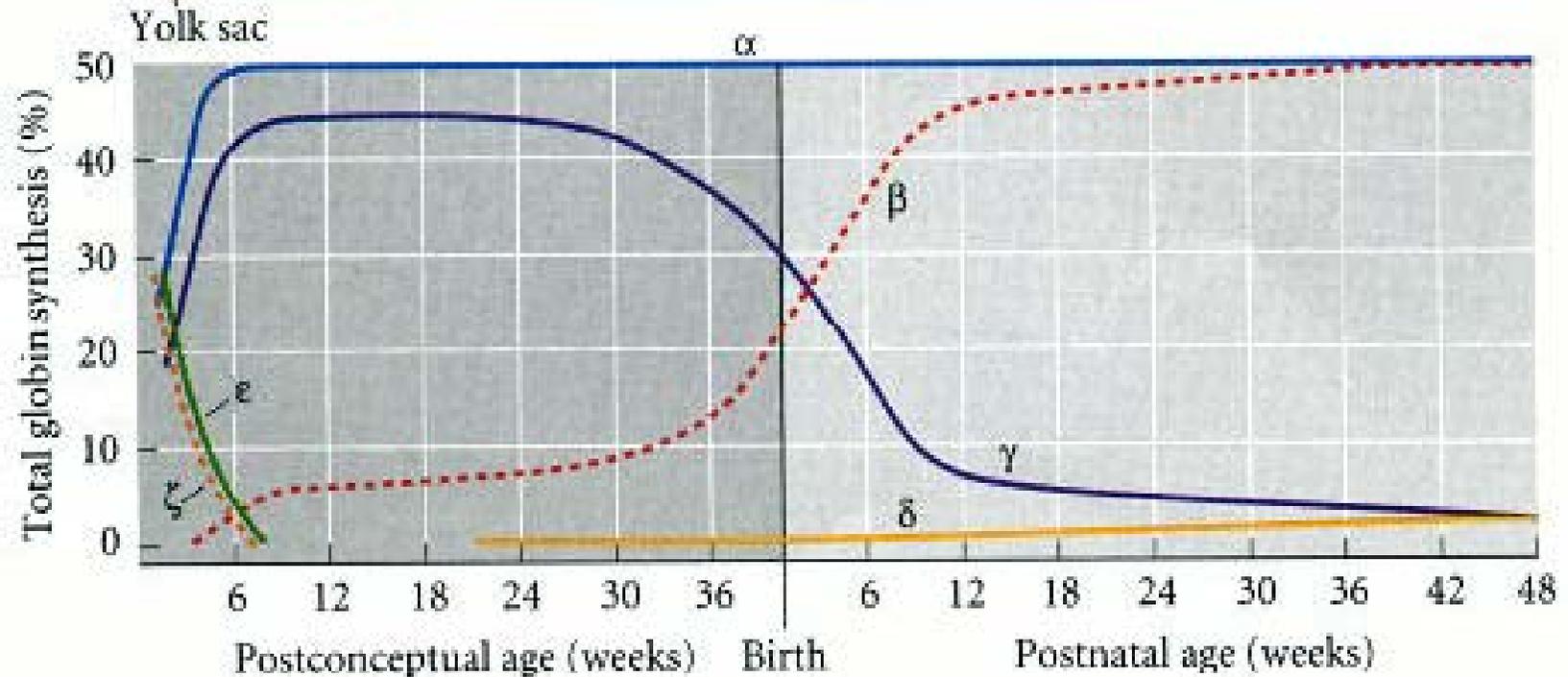
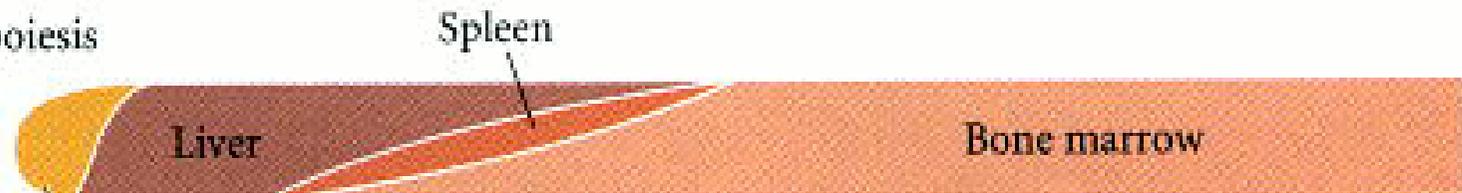
## BPG降低Hb对氧的亲合力



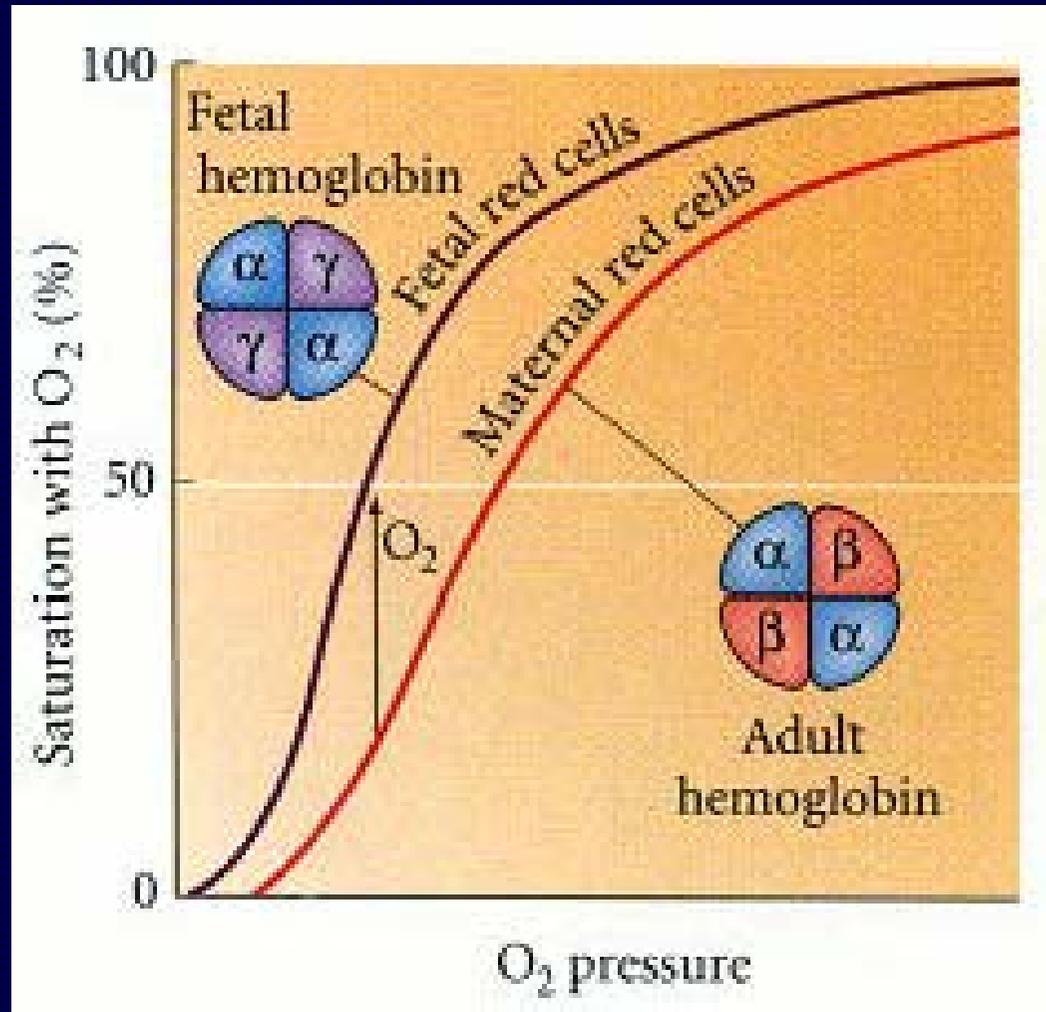
BPG: 2、3—二磷酸甘油酸

**调控亚基基因时序表达  
导致的血红蛋白氧合特征改变**

Site of erythropoiesis



人的各发育阶段血红蛋白所含亚基种类及比例

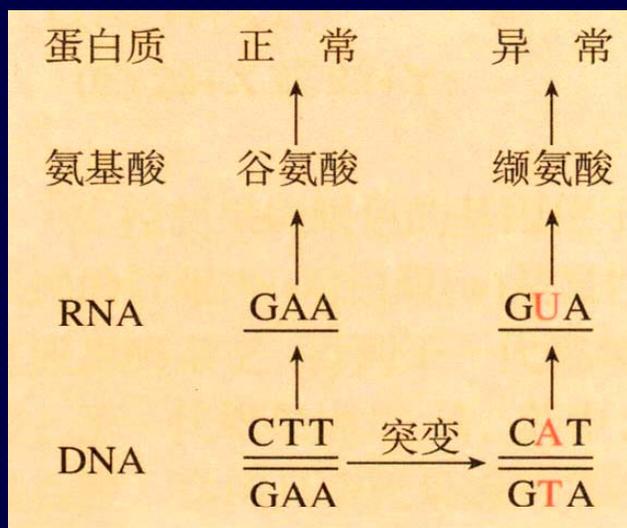


$\gamma$ 亚基与BPG的亲合性低于 $\beta$ 亚基，胎儿血红蛋白对氧气亲和力高，利于从母体血红蛋白夺取氧气

## 2、镰刀细胞型贫血症的 蛋白质结构水平成因

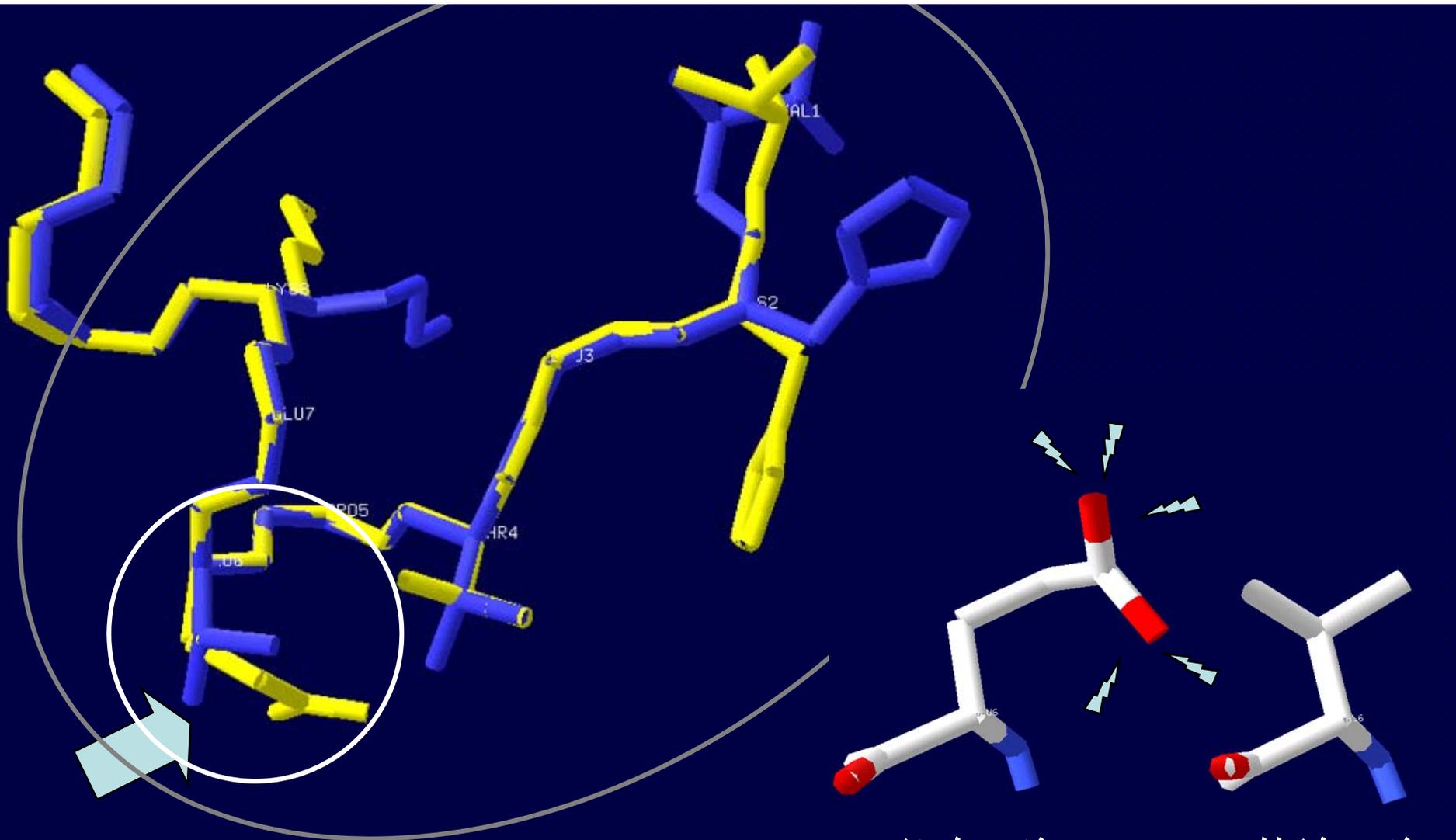
# 镰刀型细胞贫血症

- 镰刀型细胞贫血症患者的血红蛋白异常
- 血红蛋白的溶解度下降①
- 在低氧毛细血管区③，血红蛋白形成纤维结构②，导致红细胞扭曲成镰刀状(即镰变)
- 这种僵硬的镰状红细胞不能通过毛细血管，加上血红蛋白的凝胶化使血液的粘滞度增大，阻塞毛细血管，引起局部组织器官缺血缺氧，产生脾肿大、胸腹疼痛(又叫做“镰形细胞痛性危象”)等临床表现
- 此种红细胞也容易破裂造成溶血④。



镰刀型细胞贫血症病因的图解

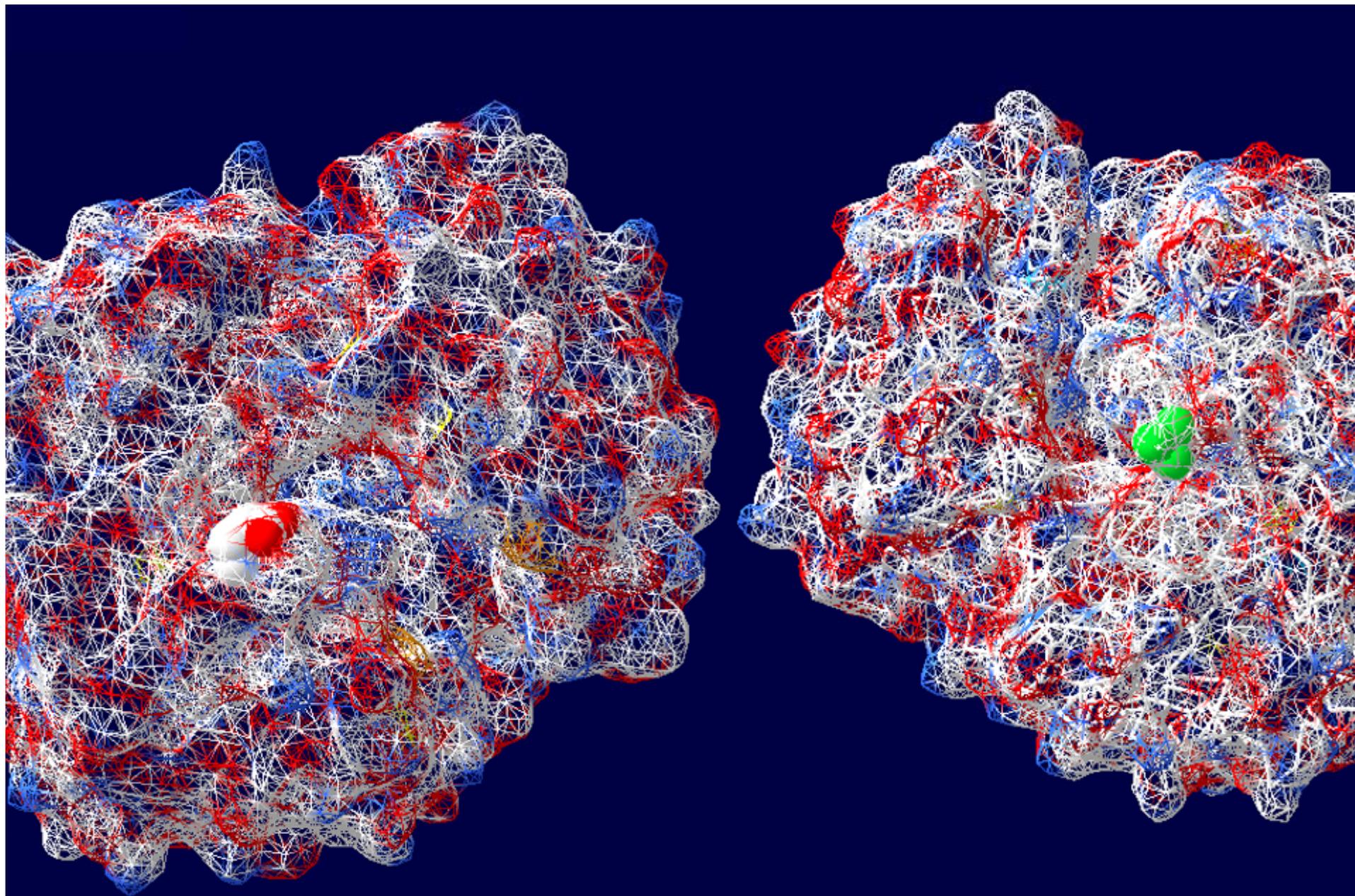
# ①变异血红蛋白表面特性及其溶解性



谷氨酸

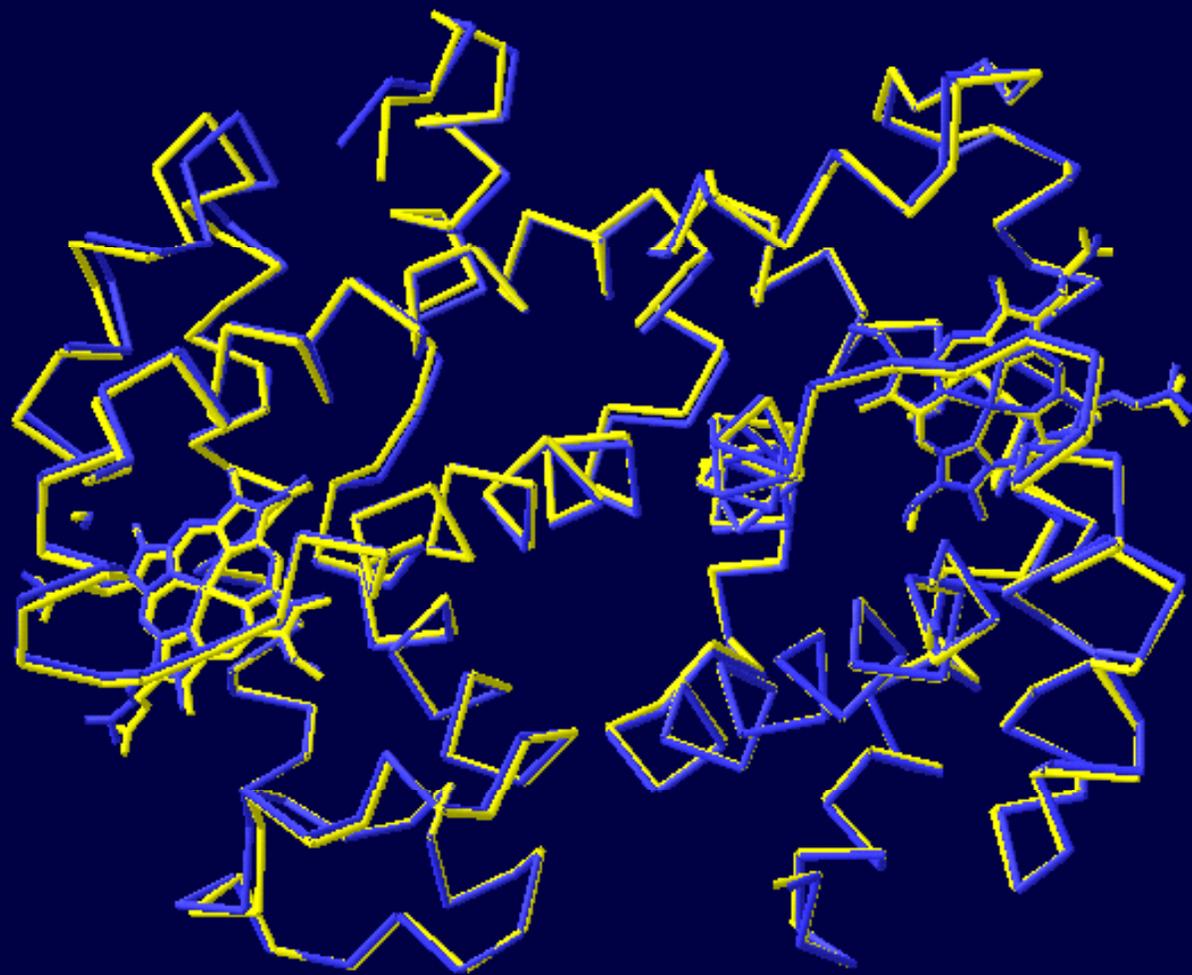
缬氨酸

主要是氨基酸残基侧链的差异



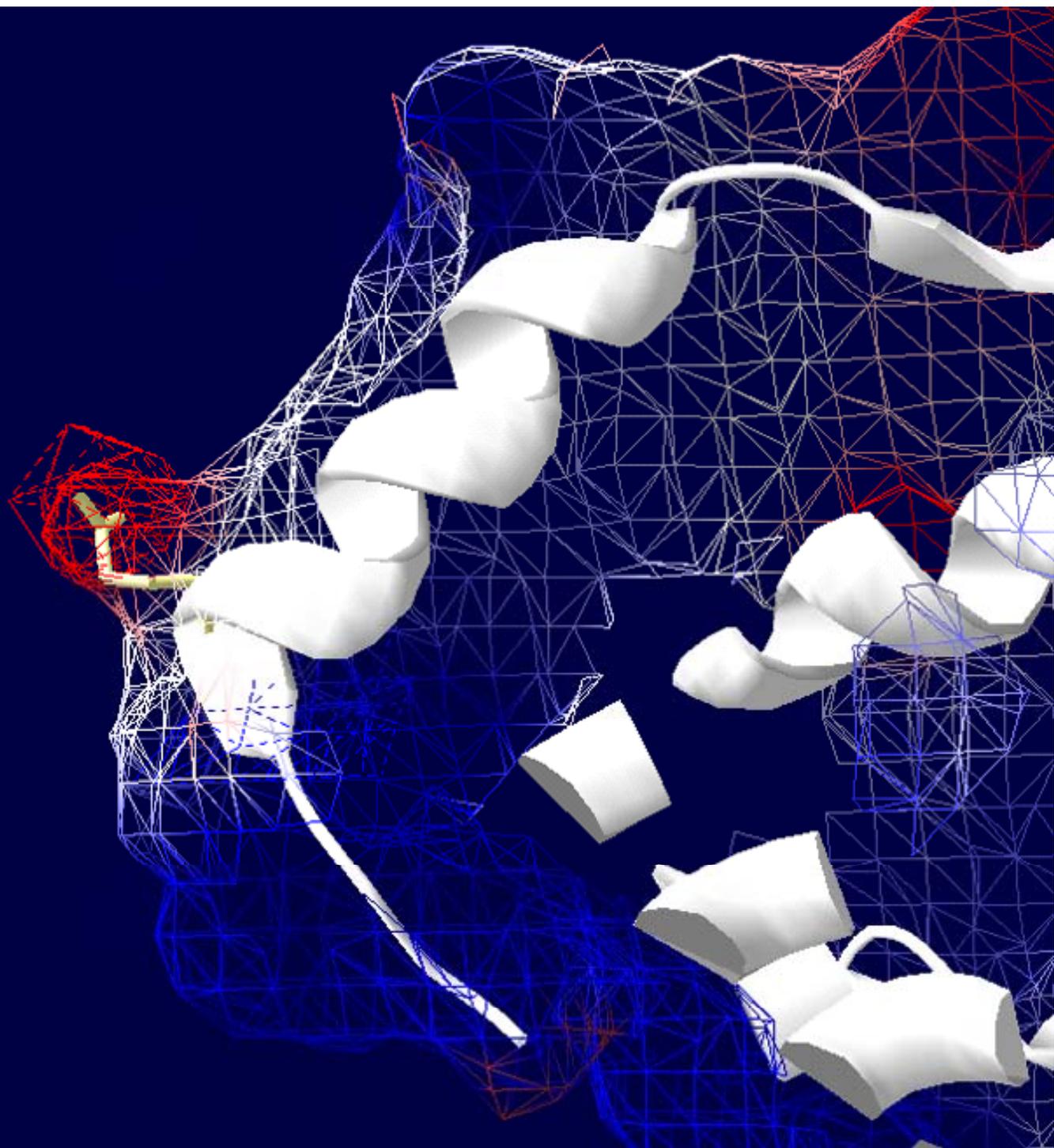
突变发生在蛋白质表面，主要影响到蛋白质表面性质，  
导致其溶解性的降低

## ②变异血红蛋白形成纤维

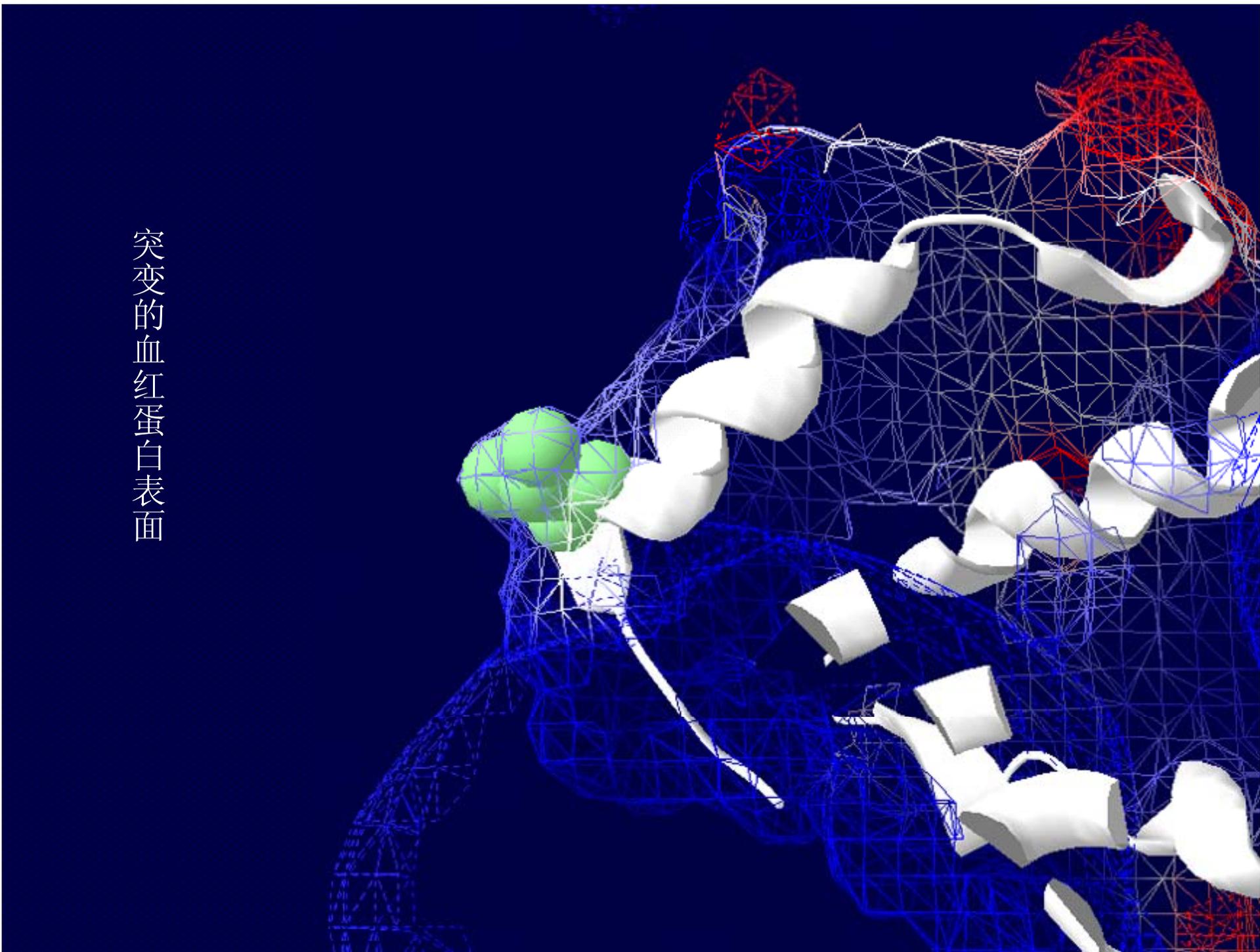


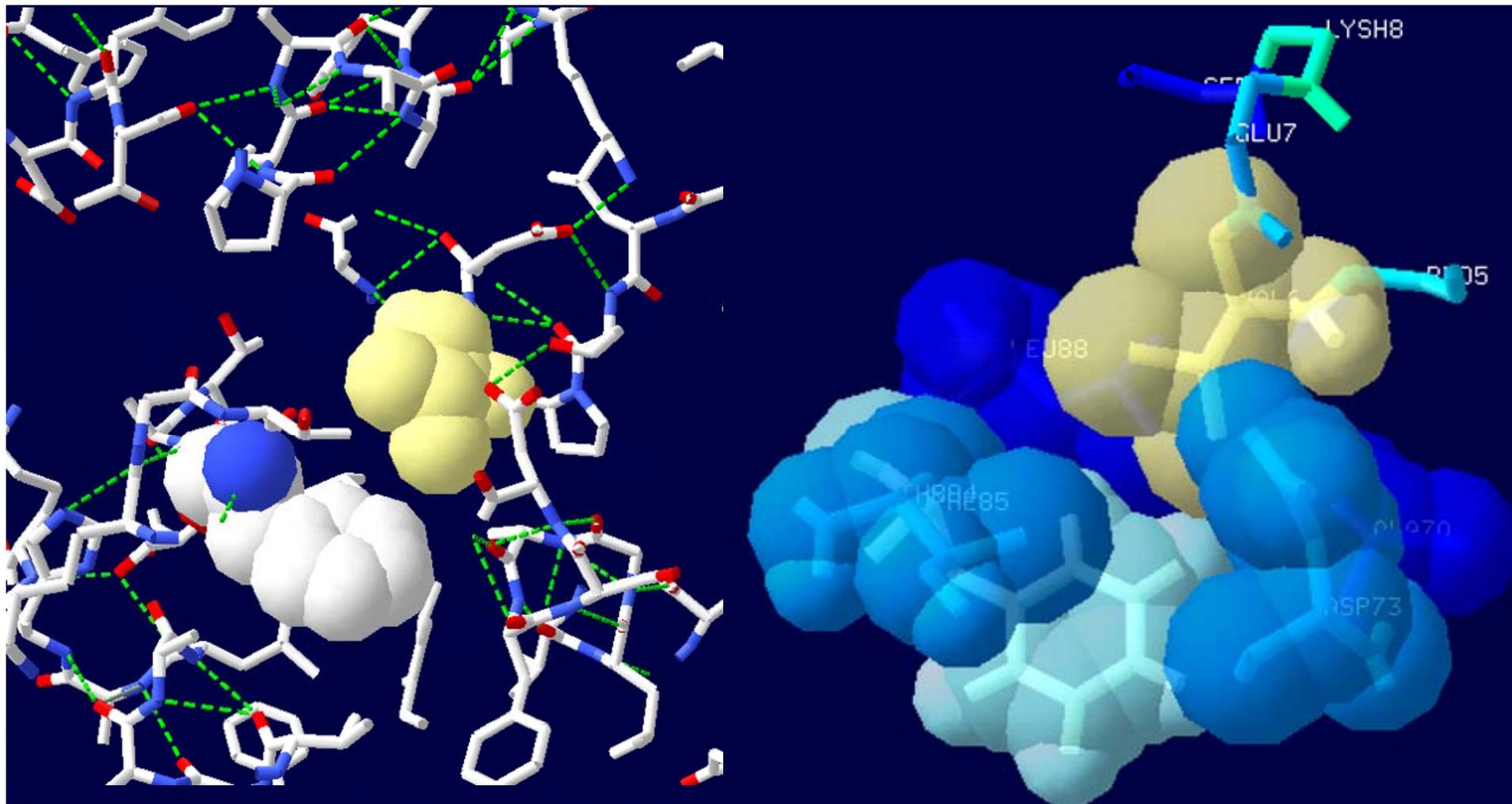
氨基酸残基的取代没有导致单个血红蛋白结构的重大变化

正常的血红蛋白表面

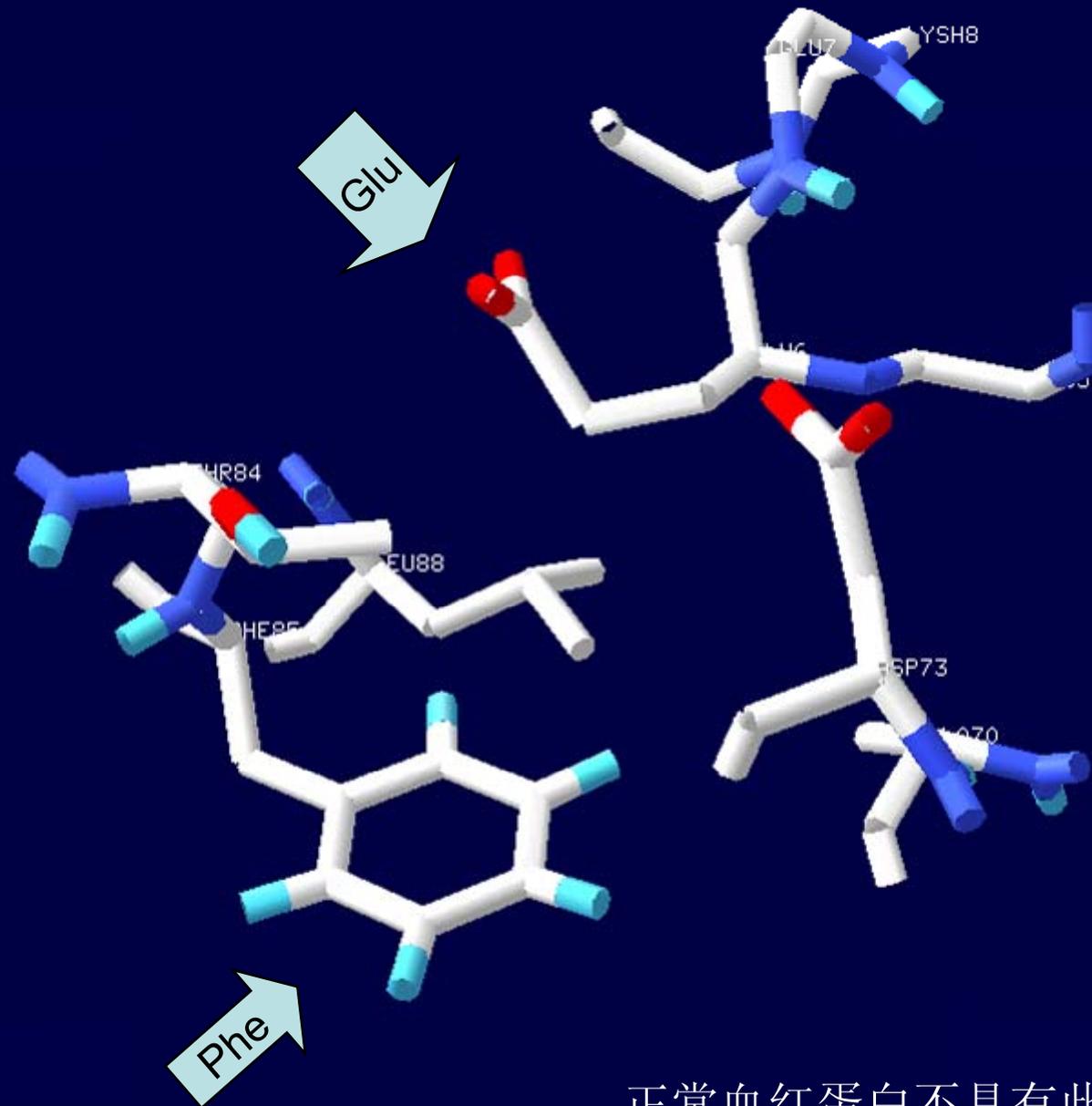


突变的血红蛋白表面

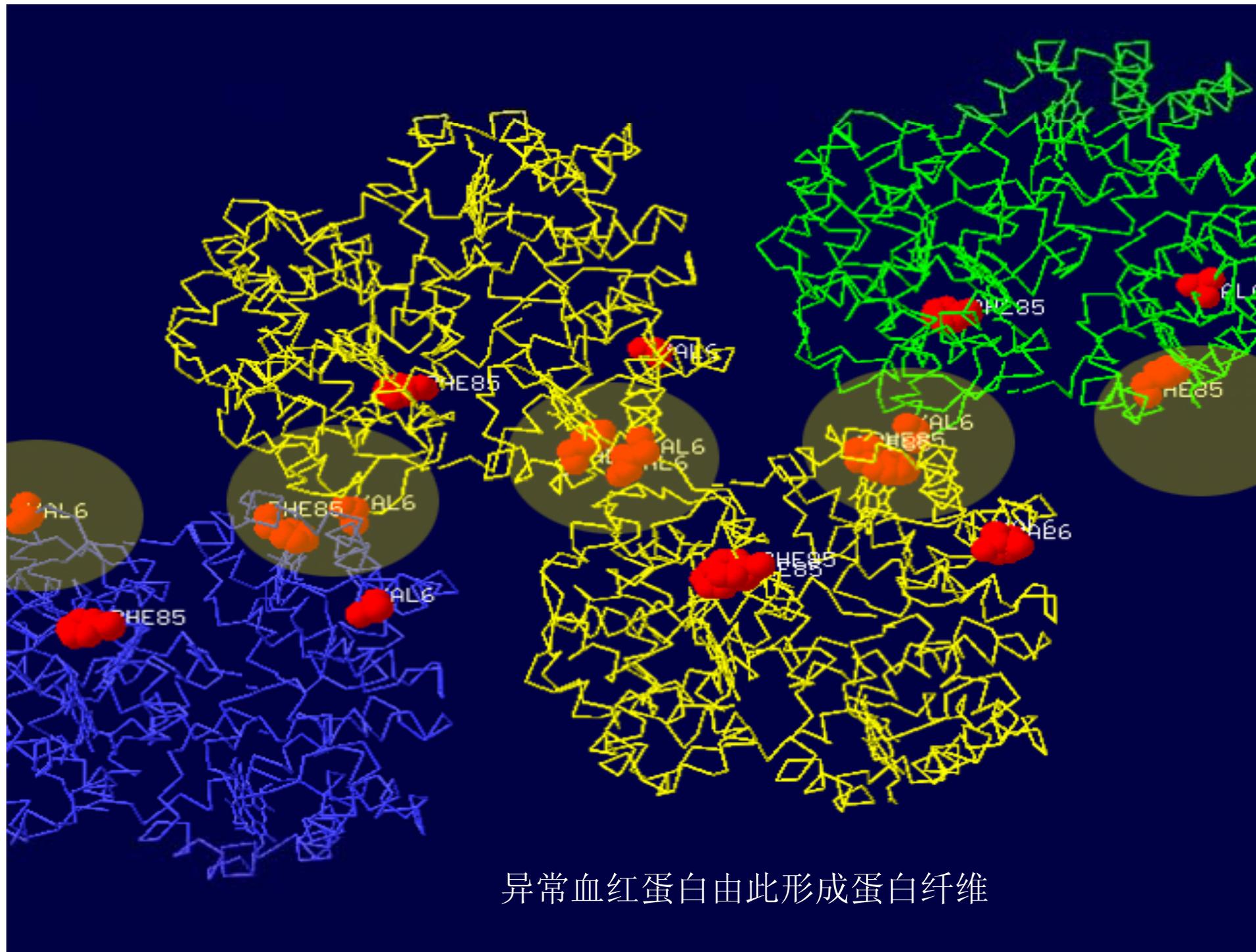




分属于不同血红蛋白的两个  $\beta$  链之间形成疏水作用力  
 $\beta$  链6位缬氨酸 与另一蛋白的  $\beta$  链85位苯丙氨酸



正常血红蛋白不具有此种关系



异常血红蛋白由此形成蛋白纤维

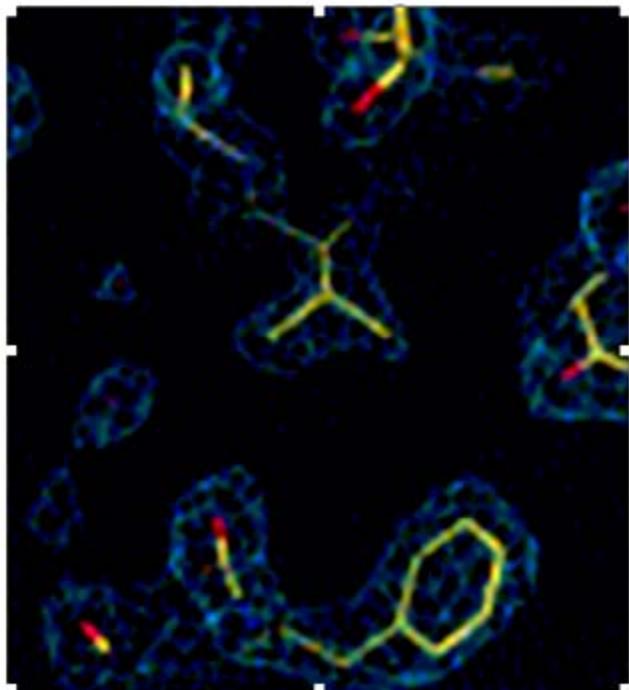
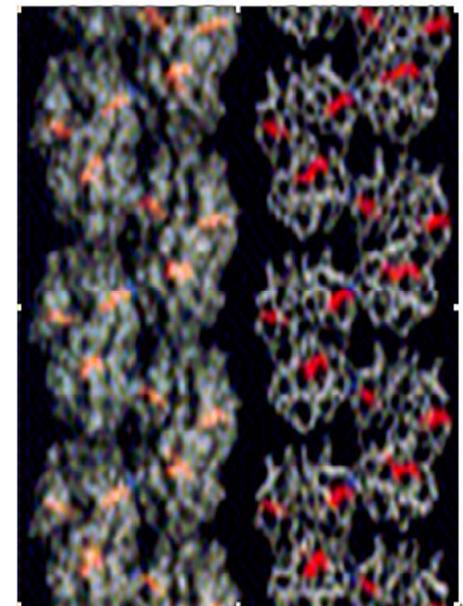
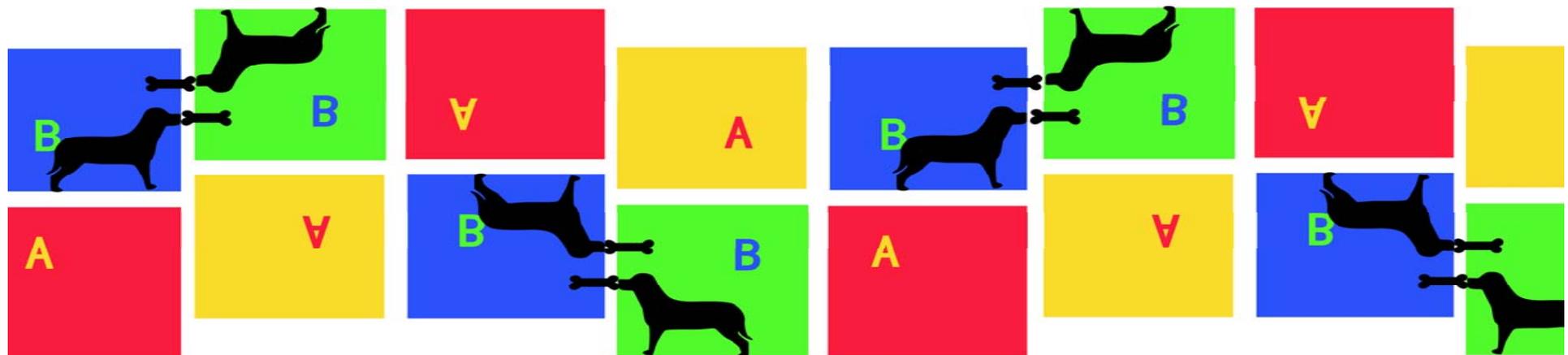
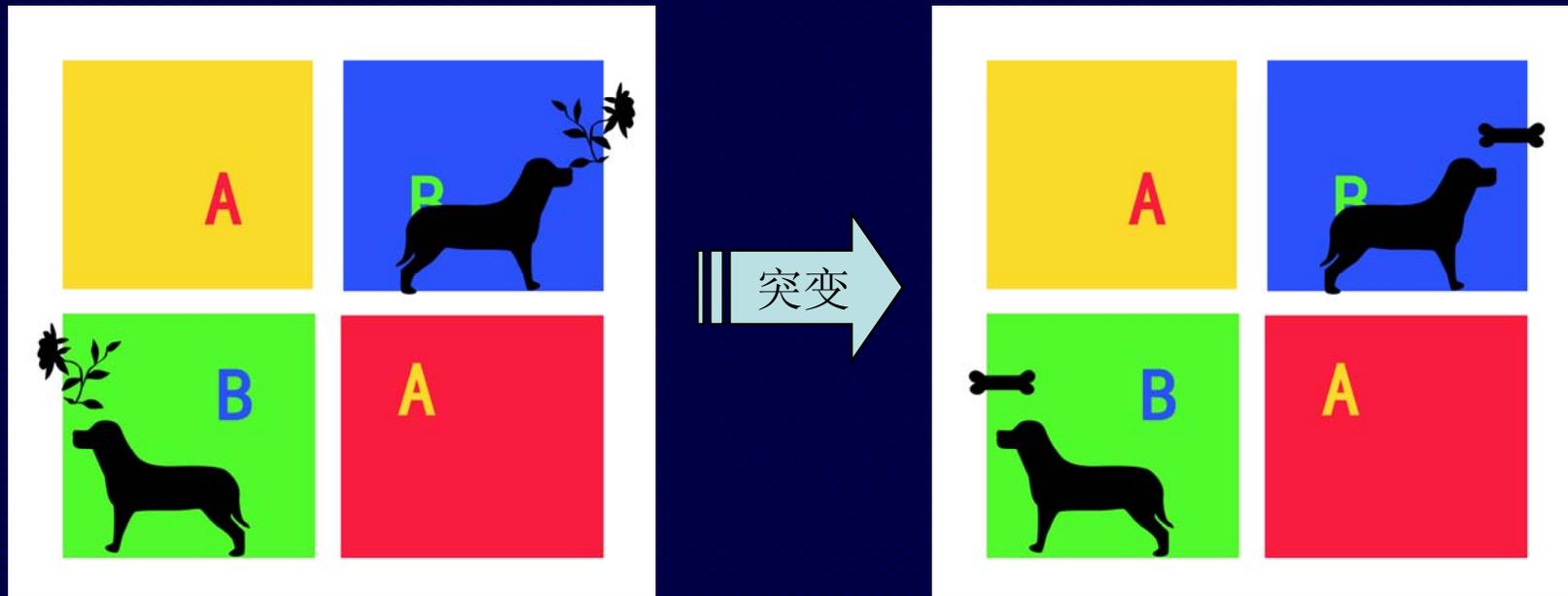


Figure 2.  $F_o - F_c$  omit map contoured at  $3.0 \sigma$  depicting the area immediately surrounding the mutant valine from the  $2\beta 2S$  chain. This residue is involved in lateral contact 1 of the crystal structure. Below and to the right of the centrally-located valine side-chain is  **$1\beta 1S$  Phe85**, part of the **hydrophobic patch** from a second tetramer with which  **$2\beta 2S$  Val6** interacts. Three water molecules are also visible to the left of the valine side-chain. (Figure generated with O, [[Jones et al 1991](#)]).

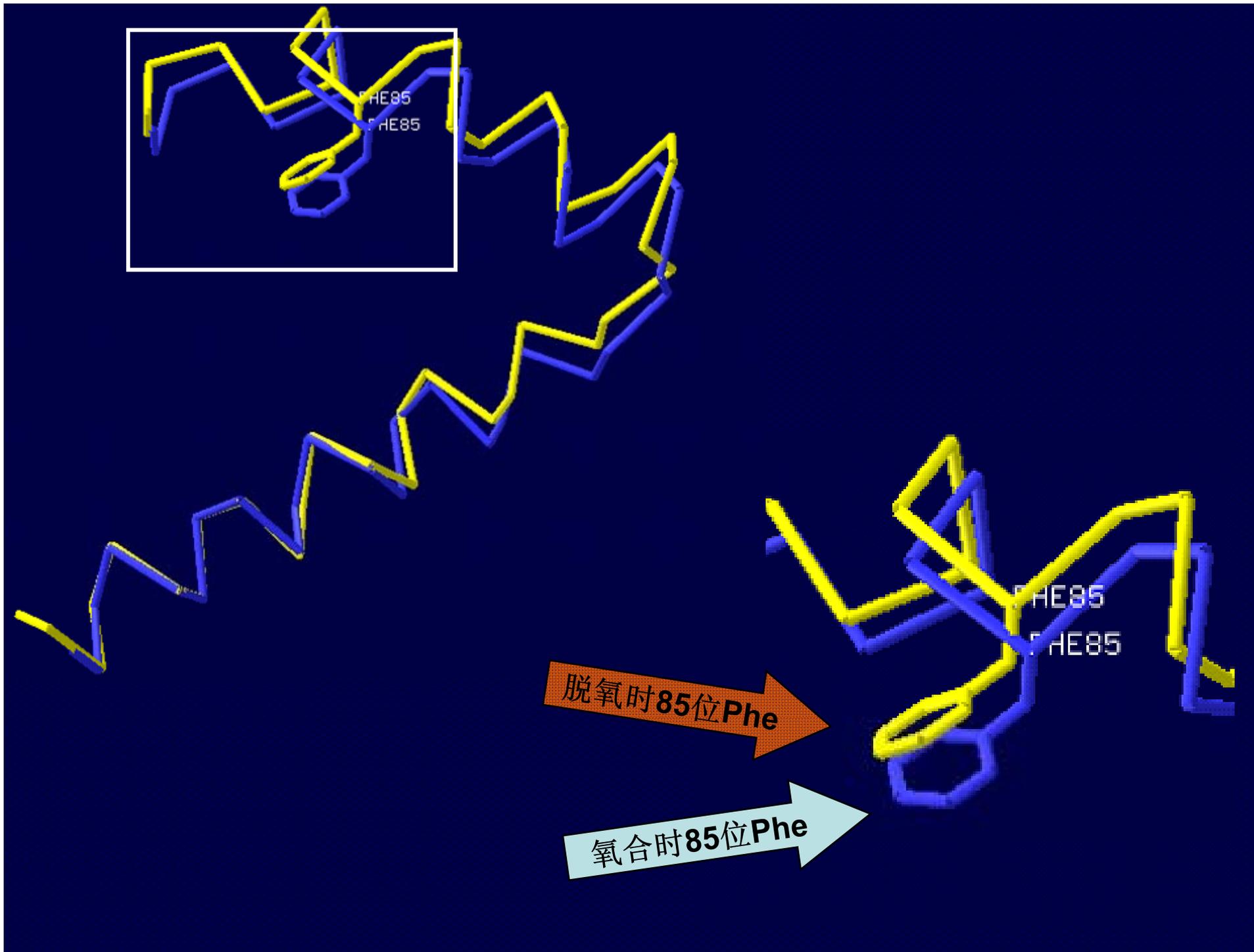
Figure 3. Two depictions of the double strand of hemoglobin molecules found in the crystal. On the left, the strand is shown as a transparent molecular surface, with heme groups colored red, and the mutant valine residues blue. In the representation on the right, the protein backbones are shown as white coils, with the color scheme for heme groups and mutant valine residues remaining the same as the left. The axial contacts are located between molecules within a single strand in the vertical direction. Lateral contacts involving the blue valine residues act to associate the two single strands into the double strand. (Figure generated using GRASP, [[Nicholls et al 1993](#)]).



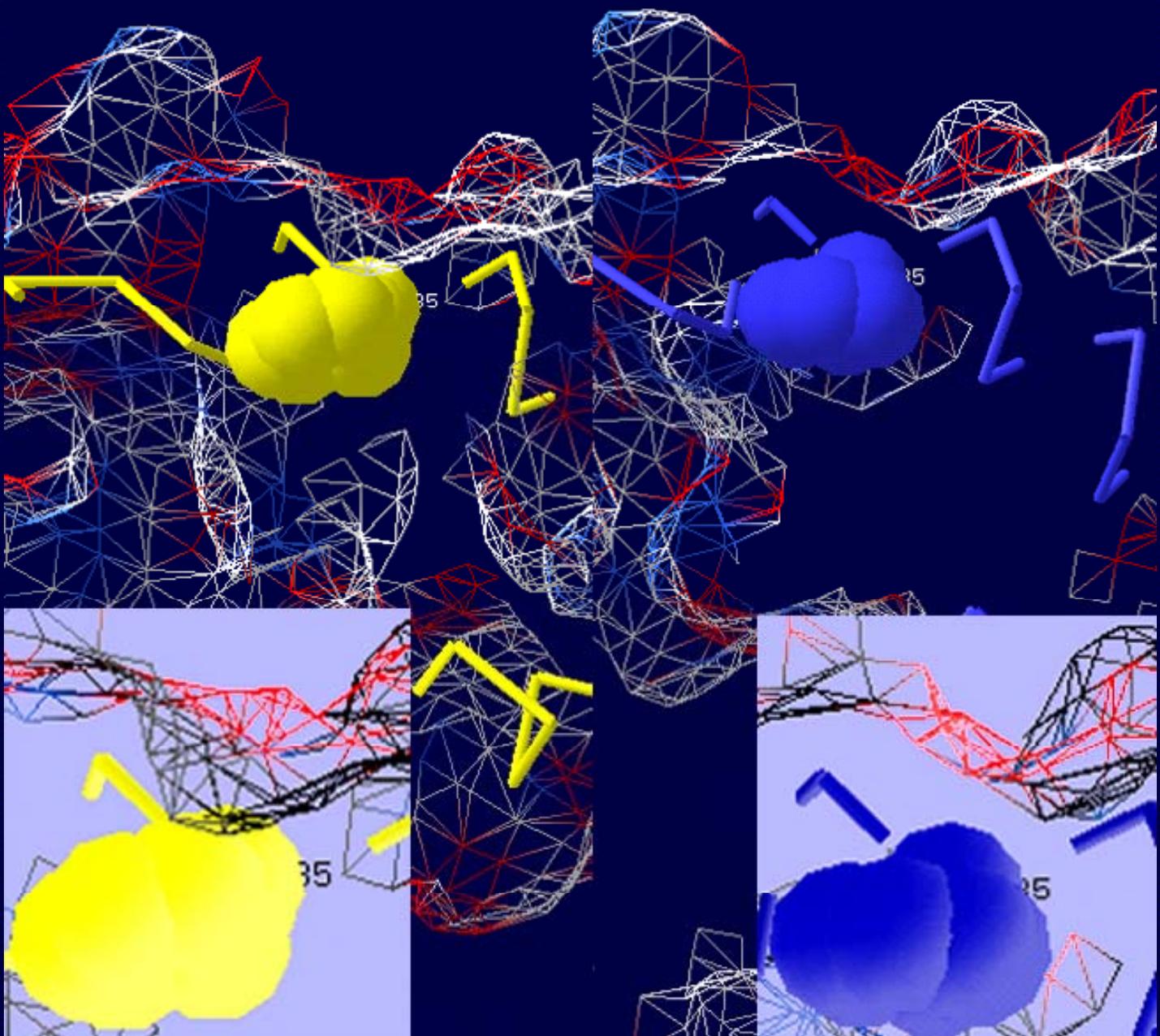
突变的 $\beta$ 链6位缬氨酸 与另一蛋白的 $\beta$ 链85位苯丙氨酸主导形成疏水作用力，使变异血红蛋白形成纤维凝胶



## ③低氧下发生形成纤维

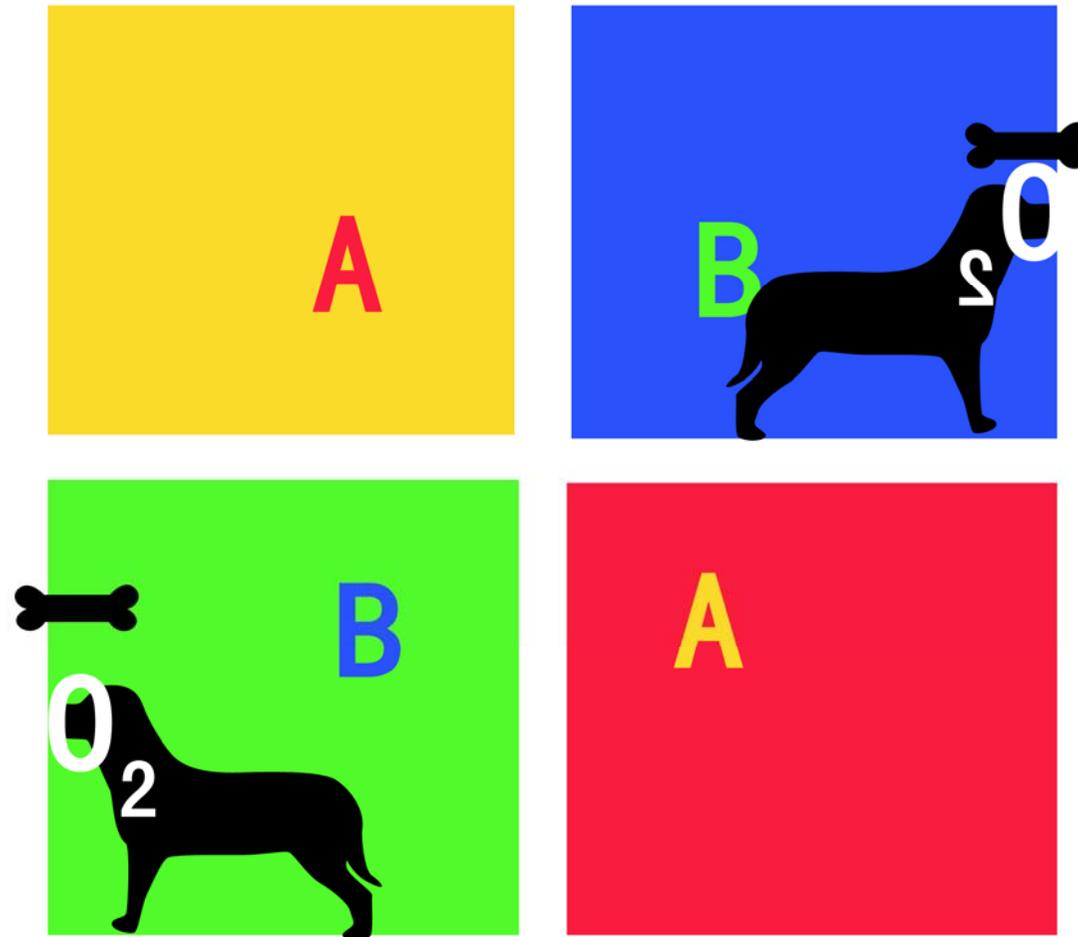


脱氧血红蛋白85位Phe位于蛋白表面



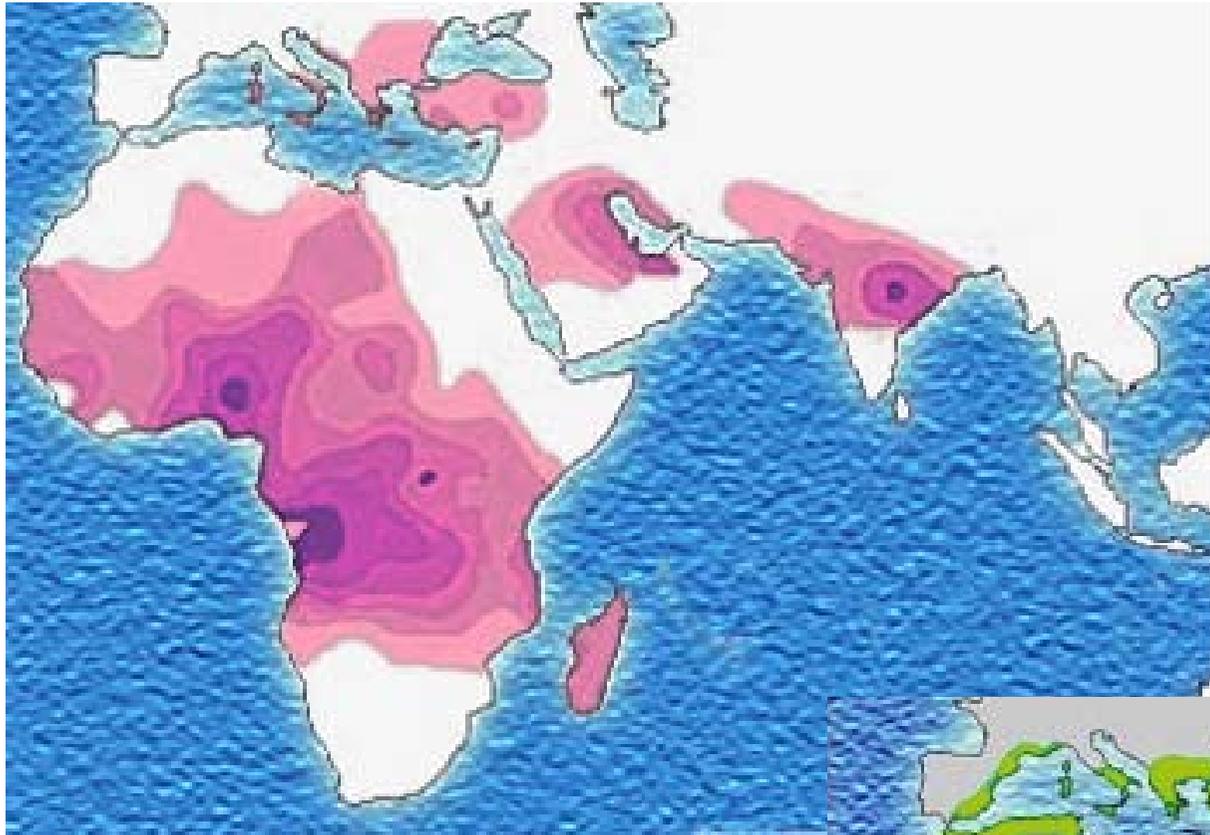
氧合血红蛋白85位Phe不参与蛋白表面形成

氧合导致 $\beta$ 链85位苯丙氨酸位置加深，埋在蛋白质分子内部，破坏了疏水作用形成条件，因此富氧区不易形成镰刀型红细胞

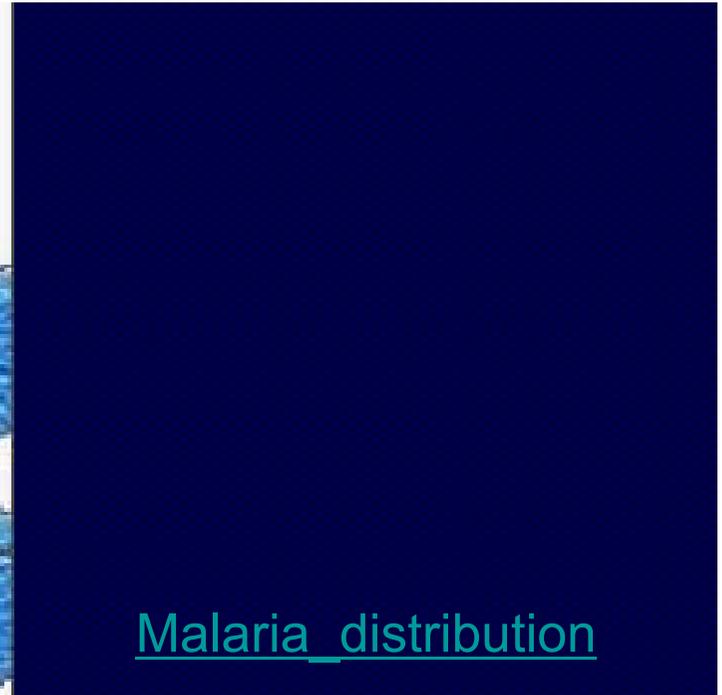


- 变异血红蛋白形成蛋白纤维还与血红蛋白的分布特殊性相关：种类单一、数量巨大
- 每个红血球含有两亿到二亿个血红蛋白分子，占红血球湿重的35%、干重量的97%
- 缺氧区二氧化碳含量高，血液含更多的氢离子和碳酸氢根离子，可能也促使了蛋白纤维的形成
- 氢离子与二氧化碳促进氧合血红蛋白脱氧，导致生成易于凝集的脱氧型异常血红蛋白
- 碳酐酶

## ④镰刀型细胞贫血症与疟疾



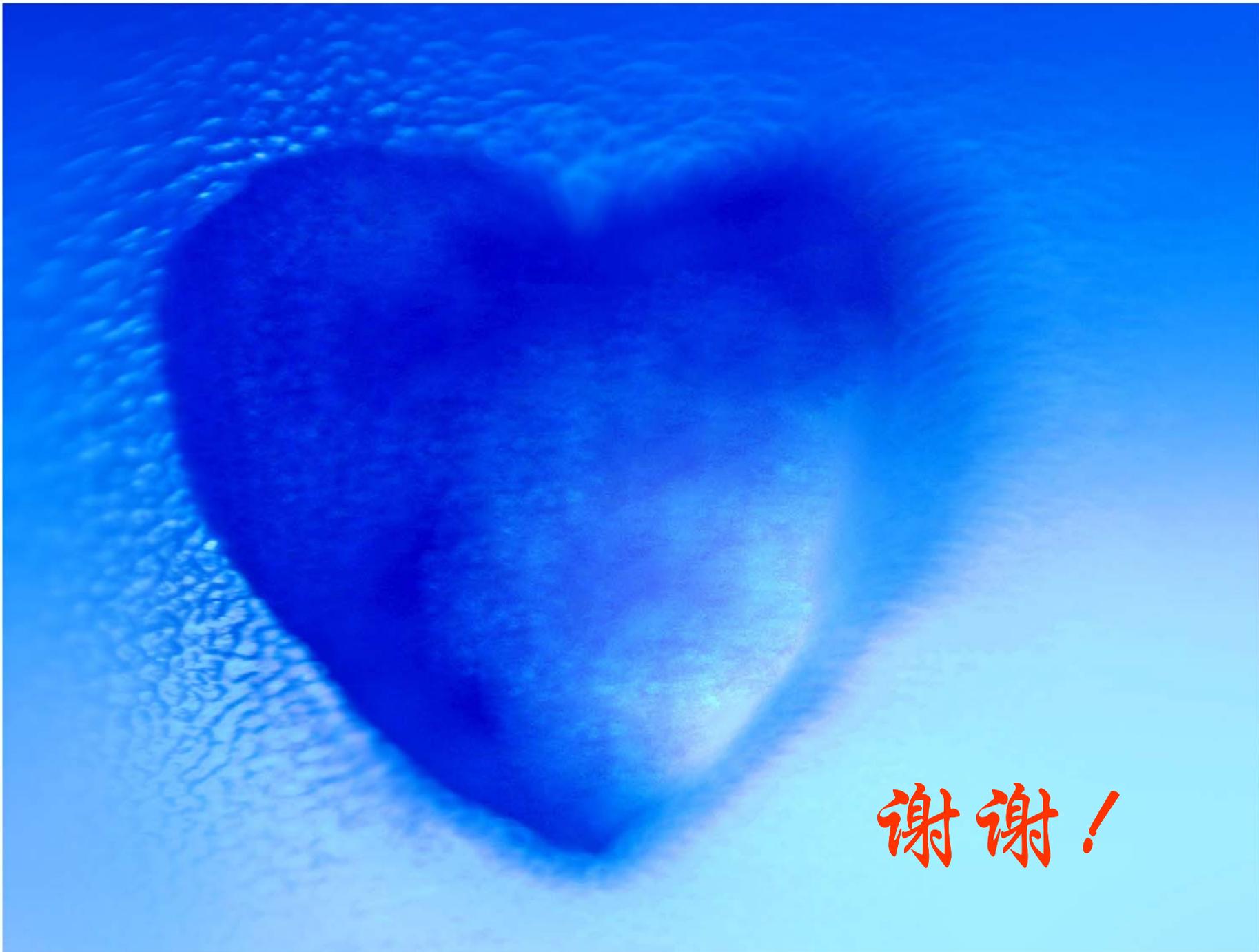
Sickle\_cell\_distribution



Malaria\_distribution



- 疟原虫具有复杂的生活周期，其中一段时期存在于红细胞内。
- 镰刀型红细胞十分脆弱，疟原虫的侵袭很容易使其崩解。导致疟原虫的原质团不能进行复制
- 疟原虫的表面抗原更迭和生殖期隐蔽在血红细胞是其逃避寄主免疫系统的重要手段
- 另外，异常的血红蛋白也使疟原虫难以定植
- 疟原虫营养及氧气匮乏
- 平衡多态性现象：纯合子致死性与杂合子抗病性



谢谢!